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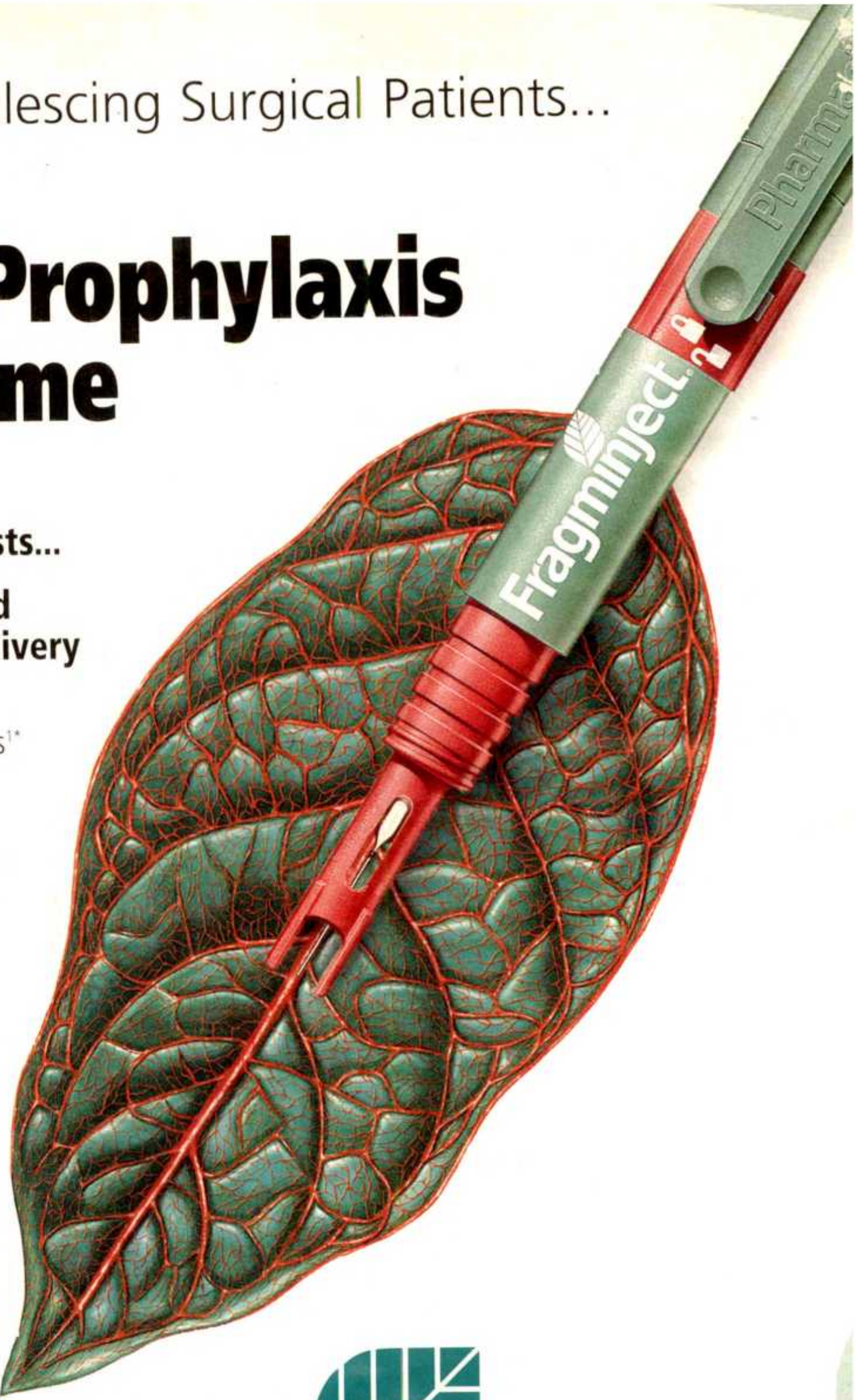

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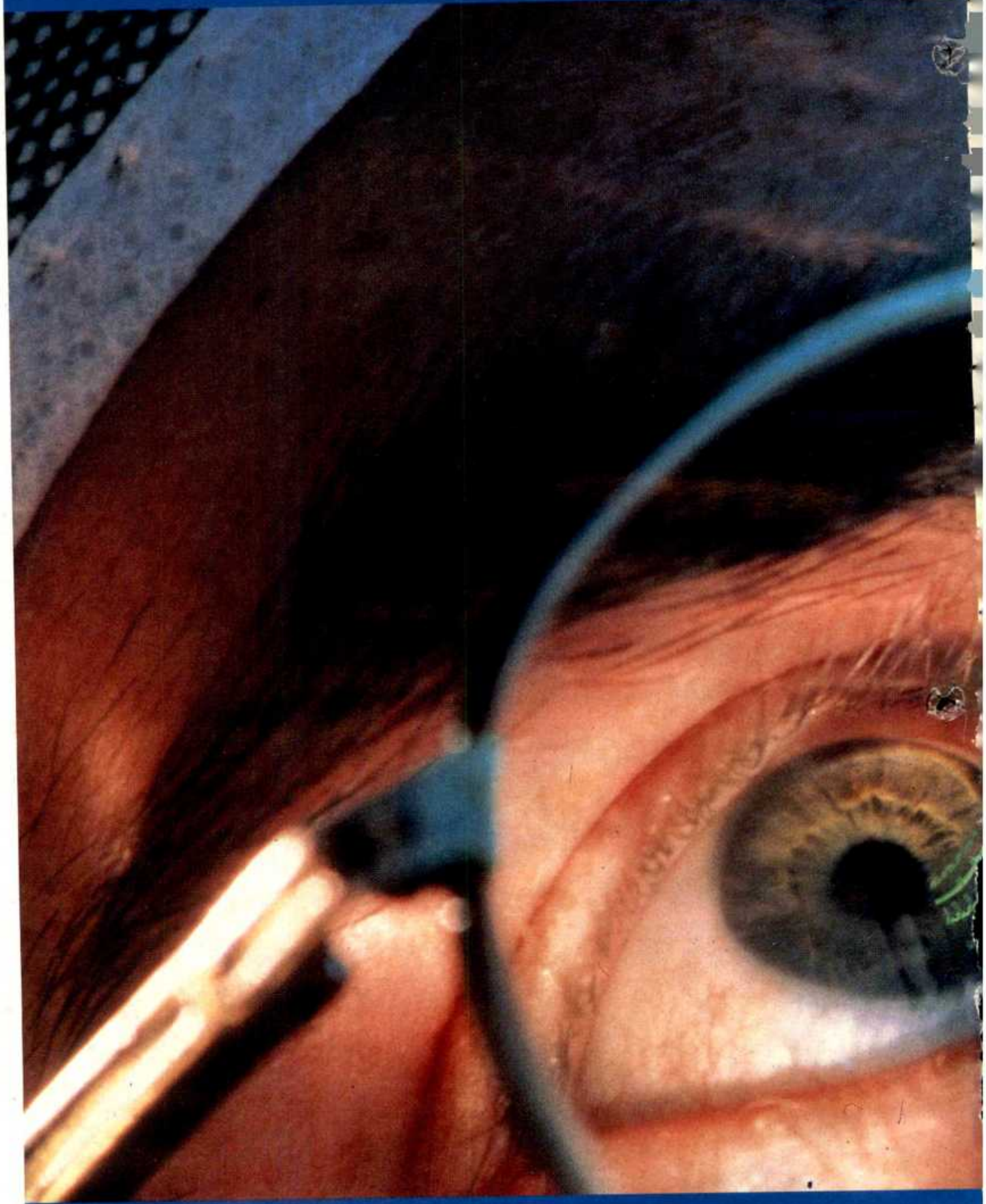

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Leading articles

Intestinal obstruction in patients with advanced malignant disease

Patients presenting with intestinal obstruction thought to be caused by a primary malignancy are generally and correctly offered surgery. However, even at presentation, a few will be unsuitable for open surgery because of associated medical conditions or signs of terminal disease. They may benefit from endoscopic or laser treatment, or need direct referral for palliative care. Difficulties arise more often when a patient with known previous malignancy re-presents with intestinal obstruction. Experienced surgeons when faced with this predicament operate with caution, as inappropriate surgery does not improve outcome. None the less, many surgeons, particularly the less experienced, feel compelled to operate on the assumption that obstruction always demands surgical intervention. We question this philosophy.

The overall mortality rate associated with surgery for acute bowel obstruction from all malignant causes is about 20 per cent[1]. This rate increases slightly when surgery is palliative and increases dramatically in malnourished patients, from 23 to 72 per cent[2]. In advanced intra-abdominal cancer the picture is worse, with a mortality rate of 26 per cent and a median survival of only 6·6 months[3]. Furthermore, the operative mortality rate increases with age from 18 per cent in patients under 50 years to 69 per cent in those over 70 years[3]. The site of primary tumour also affects surgical mortality. Colorectal cancer has the lowest rate at 13 per cent with a median survival of 10 months. Ovarian, endometrial, cervical or pancreaticobiliary primary tumours causing obstruction have a mortality rate of about 30 per cent with a median survival of 4 months[3].

Other clinical features also affect outcome. Emergency surgery increases the mortality rate threefold and, although survival may be increased by a few months, relief of symptoms has been shown to last only 2 months overall[4]. In peritonitis with a perforated obstruction the median survival is only 1 month[3]. Liver metastases alone allow a median survival of 12 months but when associated with local growth this is reduced to 2 months. Single site obstruction carries a median survival of 4·5 months compared with multiple sites for which survival is reduced to 2 months[4].

All these depressing data tend to discourage surgeons from operating, but there are some good prognostic factors. Survival is better after resection if the original tumour was of low grade or stage, and if there has been a long interval since the first operation. The well nourished patient with no evidence of secondary disease has a better prognosis. In addition, it has been shown that in about a third of patients with previous cancer the obstruction is caused by benign disease. In one review of a mixed series of 53 patients 17 (32 per cent) were found to have a benign cause[5]. A review of 92 patients with previous gynaecological cancer who presented with obstruction showed that 31 (34 per cent) had benign disease[6].

Clearly the decision to operate must be made with as much information as possible and with fully informed patient consent. In patients with advanced cancer the situation is rarely an absolute emergency, so time may be taken to inform the patient and family about the situation and determine their wishes. However, once a decision to operate has been made, surgery should be carried out without delay. The majority of patients presenting with obstruction in advanced malignancy are incompletely obstructed, and rapid assessment by clinical, radiological, endoscopic and pathological means may be required to assess the situation adequately. Barium studies, computed tomography, magnetic resonance imaging, ultrasonography, paracentesis and fine-needle aspiration cytology of suspicious nodes or extra-abdominal sites may all contribute to a proper staging of the disease. However, there is no point in proceeding with any investigation if the patient is too ill or declines surgery. Furthermore, if at the outset it is clear that surgery is contraindicated, intravenous fluids and nasogastric suction should not be started.

There is no evidence that conservative treatment leads to a sustained relief of obstruction and symptom control can be obtained in the majority of patients with appropriate medication.

Continuous subcutaneous infusion using a portable syringe driver is the preferred route of drug administration. A combination of drugs may be given to control symptoms of colic, continuous abdominal pain, nausea and vomiting, so that the patient maintains mobility and independence. If a syringe driver is unavailable, the drugs can be given by bolus injection or rectally. Colic should be treated by stopping stimulant laxatives and prokinetic antiemetics. Opioids are sometimes effective alone, but usually an antispasmodic such as hyoscine butylbromide 60–300 mg per day is required. Continuous abdominal pain is treated by titrating the dose of diamorphine (or morphine) in the syringe driver. Haloperidol 5–15 mg per day or cyclizine 150 mg per day may be used as first line treatment for nausea and vomiting. The somatostatin analogue octreotide at a dose of 0·3–0·6 mg per day[7] and hyoscine butylbromide reduce gastrointestinal secretions and motility; they are therefore effective antiemetics in this situation. Methotrimeprazine 50–150 mg per day is a sedative phenothiazine which is useful in controlling intractable vomiting in the last days of life[8].

Pharmacological treatment offers good control of pain and colic although most patients continue to vomit about once a day, but with little nausea. Patients eat and drink as they choose, the majority favouring small and low-residue meals which are mostly absorbed in the proximal small bowel. With adequate oral fluids, thirst is rarely a problem. Drug treatment is less successful in the patient with gastroduodenal or jejunal obstruction. High-dose metoclopramide, dexamethasone and octreotide sometimes help but, if these fail, a percutaneous venting gastrostomy should be considered as a better alternative to nasogastric intubation[9]. Fluids should then be given by hypodermoclysis or intravenous infusion, unless the patient is terminally ill.

The management of patients with intestinal obstruction and advanced cancer demands close cooperation between surgeons and palliative care teams.

'A surgeon is a doctor who can operate and who knows when not to'. (Theodor Kocher (1841–1917)).

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Rectal prolapse

The management of rectal prolapse should be based on an attempt to restore normal physiology. Studies indicate that prolapse is associated with reversible rectoanal inhibition, which explains sphincter recovery[1,2]. Continence restoration is dependent upon restoring a positive gradient between sphincter and rectal pressures. Many patients are constipated and this plays a significant role in the recurrence of prolapse.

Suture fixation, Ivalon (Downs Surgical, Sheffield, UK) insertion, anterior and posterior mesh rectopexy, and resection rectopexy have been compared directly[3]. All but the Ivalon technique improved continence; best results were achieved using the non-implant methods. Of 118 patients undergoing resection, including 40 treated laparoscopically, none developed a leak, confirming resection as a safe operation; there was no operative mortality. Compared with any other techniques, resection produced better results in terms of improvement in the sensation of adequate rectal emptying. Sphincter pressures increased significantly after resection and suture, but not after any form of implant.

There are many series which report excellent results in the treatment of rectal prolapse[1–7] and several involve implants to ensure rectal fixation. While resectional procedures are associated generally with the lowest recurrence rates, theoretically they carry the risk of anastomotic dehiscence. If one accepts the importance of retaining a compliant rectal reservoir, low anterior resection seems contraindicated.

As sphincter pressures only improve after non-implant surgery, resection rectopexy has become the author's procedure of choice in fit patients. The operation includes fixation after mobilization, lateral ligament division, and mobilization of the splenic flexure, with an anastomosis at 12–14 cm. In all, 49 patients have had ambulatory studies before and after this procedure. High rectal pressure waves (median 71 cmH_2O) associated with internal sphincter electromyographic inhibition and fall in anal pressure to a median of 15 cmH_2O were recorded before operation, lasting between 30 and 150 s. Similar waves have not been observed in normal subjects. During these episodes, 46 patients recorded a desire to defaecate and five were actually incontinent[2].

Recovery of continence

Ambulatory studies were carried out within 6 months of surgery in 48 patients. Incontinence was improved in 44, who became continent of solid and liquid stool. Prolapse waves disappeared and resting pressures rose, mirrored by an increase in internal anal sphincter electromyographic frequency. Furthermore, during rectoanal sampling episodes, rectal pressures no longer exceeded anal pressures. Thus, although anal pressures remained relatively low, they were adequate to cope with normal rectal events. The restoration of the sensitive anal lining to its anatomic position allowed appropriate perception of rectal contents during sampling, so unconscious soiling no longer occurred in the majority of patients. Longitudinal studies showed that pressures and internal sphincter electrical frequency rose progressively over 12 months. Thus recovery is not immediate and continuing improvement may be expected with time[2].

The mechanism of recovery of continence after surgery for prolapse has been the subject of considerable debate[1–7]. Incontinence appears to be related to profound internal sphincter inhibition together with variable external sphincter neurogenic damage[1,2]. Reported continence recovery rates following resection rectopexy vary between 40 and 85 per cent[1–6]. When all operations are considered, the variation is substantial. The objectives of surgery include elimination of prolapse and retention of a compliant rectal reservoir, functioning with an adequate sphincter. It is fascinating that continence can be restored in patients with very poor sphincter function; indeed, those with the worst function often have the most to gain[3].

After surgery, resting pressures rise, but remain similar to those of incontinent patients with no history of prolapse. Squeeze pressures do not change. Reasons for recovery appear to lie in the inverse change in which the high pressure prolapse waves are abolished, resulting in rectal pressures which no longer exceed those of the weak anal sphincter. An effective operation must, therefore, be one which allows the sphincter to recover; it should not reduce rectal compliance, since this will result in high rectal pressures. Implants, particularly Ivalon, which induce an intense fibrosis[8], render the rectum less compliant and so may adversely affect continence. Indeed, ten of 53 patients treated by implantation methods experienced poorer continence in one report[6]. Moreover, a minority of patients treated with Ivalon develop septic sequelae which cause major morbidity[8], and severe constipation is common[5]. Holmstrom *et al.*[9] observed that difficulty emptying the rectum increased from 27 to 43 per cent after the Ripstein procedure; the resultant defaecatory straining is likely to cause recurrence[10]. The rationale behind the use of Ivalon is to prevent recurrence, yet resection rectopexy is the method associated with the lowest reported rates of recurrence, so the continued use of Ivalon must be questioned. Suture fixation may be associated with a higher recurrence rate than resection, but it may be considered reasonable in poorer risk patients.

Incomplete prolapse

It is important to discriminate between intussusception of dubious significance and prolapse which reaches the anal canal with gross bulging of the perineum. Rectal examination with observation of the posterior rectal wall during straining, using a sigmoidoscope in the rectum between 10 and 15 cm from the anal margin, is a useful test. Urgency as a symptom is more commonly associated with sphincter weakness, whereas patients with prolapse report soiling or voiding with no warning. A good squeeze pressure favours treating the prolapse, especially if ultrasonography confirms that the anterior sphincter is intact. The decision is often difficult but, overall, if prolapse predominates it is advisable to repair it before considering sphincter surgery.

Perineal procedures

Operations which remove the rectal reservoir, such as perineal rectosigmoidectomy, or which reduce its capacity, such as the Delorme procedure, will lead to a non-compliant neorectum; continence cannot be expected to improve to the same extent as with abdominal rectopexy. Rectosigmoidectomy removes the rectum and often very narrowed diverticular sigmoid colon is anastomosed to the anus. The Delorme procedure narrows the rectum significantly. While both these operations are considerably less invasive than abdominal surgery, and so may benefit the unfit, they are associated with high recurrence rates. The perineal operations remove the rectal reservoir and leave the patient with a high pressure, relatively non-compliant rectum, which will overcome a weakened sphincter. Deen *et al.*[4] randomized patients with incontinence and rectal prolapse to abdominal resection rectopexy with pelvic floor repair from above, or to perineal rectosigmoidectomy and pelvic floor repair from below. The functional and physiological outcome was superior in the former group. Attempts at improving the results of perineal operations by incorporating J reservoirs seem attractive.

The future

Rectal prolapse is one of the conditions that most surgeons agree is suitable for treatment using laparoscopic techniques. The prolapse may be sutured or implants inserted laparoscopically. However, longer follow-up is still needed to ensure the results are comparable to those of open operation. In a personal series of 40 patients, the functional outcome following laparoscopic rectopexy was similar to that of open surgery. Two ureteric leaks occurred early in the series, one requiring ureteric reimplantation. Four procedures were converted to open operations and the median postoperative hospital stay was 4 days.

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Review

Malignant ascites

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Investigation and treatment of malignant ascites are often in the hands of the general surgeon and can be difficult. This article considers the aetiology and pathophysiology of malignant ascites and explores the best form of management. Established treatment modalities and new therapeutic options are reviewed and a new management regimen based on a knowledge of the tumour of origin is proposed, which aims to balance potential benefit against morbidity.

Malignant ascites accounts for around 10 per cent of all cases of ascites[1]. It is a manifestation of advanced malignant disease and is associated with a poor prognosis. In about 50 per cent of patients the symptoms of ascites will be the presenting feature of their disease[2] and, since these symptoms are often non-specific, the patients may present to a variety of medical and surgical specialists.

Despite the poor prognosis of this condition, patients often require treatment for symptomatic relief and, in some cases, treatment may improve survival. As malignant ascites may relate to a heterogeneous group of conditions, correct management hinges on patient selection, balancing the morbidity of the treatment against its potential benefit. This article discusses the pathophysiology of malignant ascites, reviews the standard therapeutic options and considers new methods of treatment which offer the hope of improved palliation.

Aetiology

Malignant ascites is usually caused by intra-abdominal tumours. Ovarian cancer is the commonest primary tumour in most series[3–6] and accounts for 30–54 per cent of cases. Other common primary sites are pancreas, stomach and uterus, with breast, lung and lymphoma representing the commonest extra-abdominal sites[2,5,6]. Overall duration of survival is poor, averaging about 20 weeks from the time of diagnosis[2,6], but this is markedly dependent upon the tumour of origin. The mean survival for ovarian cancer is 30–35 weeks and for tumours of lymphatic origin 58–78 weeks, whereas for cancers of the gastrointestinal tract the mean survival is only 12–20 weeks.[2,7] In a large number of patients with malignant ascites the primary tumour is unknown. This subgroup is second only to the ovarian group in size, accounting for between 13 per cent[5] and 22 per cent[4] of cases. The prognosis in this group of patients is generally poor, but it does vary greatly, from a median of 7·5 days[4] to 3 months[7] in different series.

Pathophysiology

In healthy subjects there is a constant movement of fluid into (influx) and out of (efflux) the peritoneal cavity. By injecting ^{131}I-labelled human serum albumin into the peritoneal cavity of healthy volunteers and measuring the accumulation of ^{131}I in plasma, the transfer rate has been calculated[8] to be 4–5 ml h^{-1}. The ability of the healthy subject to resorb fluid is much greater than the fluid generated[9], with the result that there is normally only a small volume of fluid in the peritoneal cavity (approximately 50 ml)[8]. The development of ascites is due to changes in both the influx and the efflux, resulting in a net accumulation of fluid in the peritoneal cavity.

Efflux

The efflux of fluid from the peritoneal cavity has been studied extensively in mice by means of intraperitoneally injected india ink[10]. From this work it appears that the diaphragmatic lymphatics are the main pathways for drainage of peritoneal fluid, with the omental and peritoneal lymphatics and the thoracic duct playing only a minor role[11,12]. In mice with malignant ascites, india ink injected into the peritoneal cavity fails to be transported into the lymphatics and so lymphatic obstruction has been put forward as a major factor in the pathogenesis of the condition[13].

Feldman and co-workers[14] showed that ^{51}Cr-labelled erythrocytes injected intraperitoneally appeared in the peripheral blood within 5 h in normal mice. However, in mice inoculated intraperitoneally with tumour cells from a C3H mouse ovarian tumour, the fraction of radioactivity reaching the peripheral blood was reduced and, by 6 days after inoculation, no ^{51}Cr-labelled erythrocytes reached the blood stream. These events preceded the development of ascites, and the presence of tumour infiltrating the lymphatics was demonstrated on subsequent histological examination. Thus it was concluded that lymphatic obstruction by tumour precedes the development of ascites and is likely to be a major factor in its development.

More recently, similar work performed using both ^{51}Cr-labelled erythrocytes and ^{125}I-labelled human serum albumin showed that, although a marked reduction in efflux occurred during the first 5 days after tumour inoculation[15], once ascites was clinically present there was an increase in efflux which correlated with increasing hydrostatic pressure. This supports the results of Zink and Greenway[16] who found that fluid absorption from the peritoneal cavity was directly proportional to intraperitoneal pressure.

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There is also good evidence in human subjects to show that lymphatic obstruction plays a major role in malignant ascites. Coates and colleagues[17], using the technique of lymphoscintigraphy with ^{99m}Tc–sulphur colloid, showed that 32 of 38 patients with malignant ascites had no activity above the diaphragm after intraperitoneal injection of the isotope. This contrasted with the control group of 14 patients, with either no ascites or non-malignant ascites, in whom only one had no activity.

Influx

Reduction in efflux of fluid from the peritoneal cavity cannot be the only reason for the genesis of ascites because the overall flow rate is much higher in patients with malignant ascites. Using ^{131}I-labelled albumin, Hirabayshi and Graham[8] calculated the transfer rate to be between 31 and 80 ml h^{-1}, more than ten times normal. Nagy and colleagues[15] also studied influx of fluid into the peritoneal cavity in mice. They found that, after inoculation with tumour cells intraperitoneally, influx remained unchanged for several days, then rose between 5 and 7 days to values 13–25 times normal. By 7–10 days influx had risen sufficiently to exceed efflux, resulting in the net accumulation of fluid[15].

The composition of peritoneal fluid in malignant ascites is also markedly different from that found in healthy subjects. The protein content is approximately 85 per cent of plasma levels (exudate), while the protein content of normal fluid is only 20–25 per cent of plasma levels (transudate)[15]. As albumin is a prominent component of tumour ascites and accumulates in a proportion similar to that found in plasma, the substantially increased protein content of tumour ascites is likely to be due to increased permeability of microvessels to albumin rather than the local release of tumour-associated proteins. These 'leaky' vessels may either be the vessels that line the peritoneal cavity[2,8] or the newly formed vessels that form the tumour circulation[18]; the former theory demands the presence of a 'vascular permeability factor' secreted by the tumour. Such a factor, which appears to be identical to vascular endothelial growth factor, has been demonstrated in human ascites, and in the peritoneal wall of mice and guinea-pigs[15,19,20].

It has also been postulated that a raised venous pressure contributes to the formation of ascites. Raised portal vein pressures have been demonstrated in patients with ascites[8], but Zink and Greenway[21] showed that raising the portal pressure in cats did not lead to ascites if the hepatic venous pressure remained normal. However, when hepatic venous pressure was raised, this did produce a constant flow of ascites. From this evidence they concluded that filtration of fluid out of the liver sinusoids causes ascites when venous pressure is raised, rather than leakage from the intestinal vascular bed.

Hepatic vein pressure correlates closely with plasma renin concentration and plasma renin activity in patients with cirrhosis[22]. Furthermore, raised plasma renin concentration leads to sodium conservation by the kidneys via the renin–angiotensin–aldosterone pathway, and this in turn leads to water retention and ascites[22]. Raised renin concentrations have been described in some patients with malignant ascites[23] and these patients showed a good response to the aldosterone antagonist spironolactone. It has also been shown that malignant ascites in the presence of massive hepatic metastases is most likely to respond to spironolactone[24]. Thus, liver metastases causing hepatic vein obstruction may be an important aetiological factor in some cases of malignant ascites. The development of malignant ascites is probably dependent on a combination of the factors mentioned above, with each factor playing a greater or lesser role in each individual patient.

Diagnosis

It can be difficult to differentiate between ascites of malignant origin and other causes of ascites (*Table 1*) and the following modes of investigation may be useful: (1) clinical history and examination; (2) tumour markers; (3) radiology; (4) cytology; (5) biochemical composition of ascites; (6) laparoscopy.

Clinical history and examination

The main clinical symptoms of ascites include abdominal distension, continuous abdominal discomfort or pain, and anorexia which is often accompanied by nausea and occasionally by vomiting[5]. Other symptoms include shortness of breath, ankle oedema, decreased mobility and fatigue. A change in weight is also common, but this may be weight gain as a result of retention of ascites or weight loss resulting from the underlying malignant disease. Williams and Simel[25] found abdominal distension and ankle swelling to be the two commonest clinical features in patients with ascites in general.

The same workers also examined reliability of physical signs in the diagnosis of ascites. The main signs were abdominal distension, bulging flanks which were dull to percussion, shifting dullness and a fluid wave. They examined the sensitivities and specificities of the individual tests and showed that a fluid wave was the most specific at 90 per cent, but the least sensitive at 62 per cent. The other tests performed similarly, with sensitivities around 80 per cent and specificities around 65 per cent. Williams and Simel[25] concluded that a combination of signs would be most likely to lead to the correct diagnosis as no single clinical test was accurate enough when used alone.

Tumour markers

Because of a low specificity, tumour markers cannot be used to diagnose malignant disease. However, if a tumour marker were specific for a particular tumour, it would be

Table 1 Pathophysiological classification of ascites

Raised hydrostatic pressure
Cirrhosis
Congestive heart failure
Congestive pericarditis
Inferior vena cava obstruction
Hepatic vein obstruction (Budd–Chiari syndrome)
Decreased osmotic pressure
Nephrotic syndrome
Protein-losing enteropathy
Malnutrition
Cirrhosis or hepatic insufficiency
Fluid production exceeding resorptive capacity
Infections (bacterial, tuberculosis, parasitic)
Neoplasms

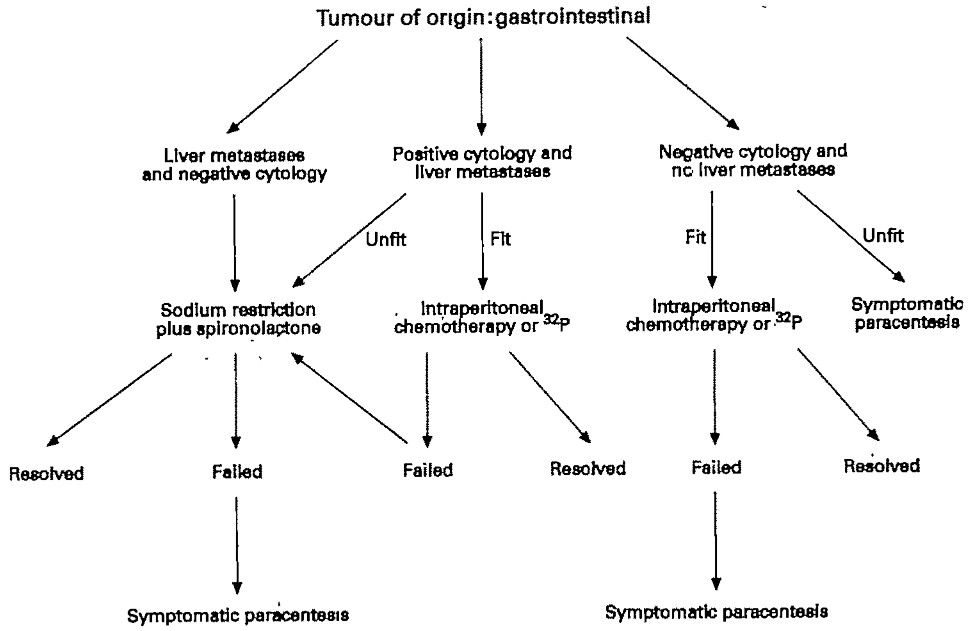
Tumour of origin: gastrointestinal
Liver metastases and negative cytology
Positive cytology and liver metastases
Negative cytology and no liver metastases
Unfit
Fit
Fit
Unfit
Sodium restriction plus spironolactone
Intraperitoneal chemotherapy or ^{32}P
Intraperitoneal chemotherapy or ^{32}P
Symptomatic paracentesis
Resolved
Failed
Failed
Resolved
Failed
Resolved
Symptomatic paracentesis
Symptomatic paracentesis

Fig. 1 Treatment of malignant ascites of gastrointestinal origin

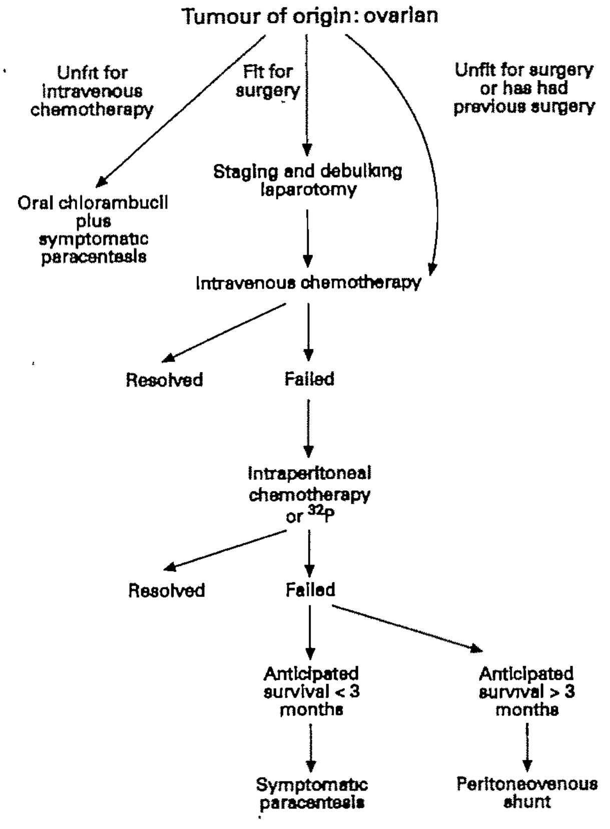
Tumour of origin: ovarian
Unfit for intravenous chemotherapy
Fit for surgery
Unfit for surgery or has had previous surgery
Staging and debulking laparotomy
Oral chlorambucil plus symptomatic paracentesis
Intravenous chemotherapy
Resolved
Failed
Intraperitoneal chemotherapy or ^{32}P
Resolved
Failed
Anticipated survival < 3 months
Anticipated survival > 3 months
Symptomatic paracentesis
Peritoneovenous shunt

Fig. 2 Treatment of malignant ascites of ovarian origin

very useful in diagnosing the primary neoplasm in malignant ascites.

Carcinoembryonic antigen (CEA) in blood is used primarily to detect relapse in patients with colorectal carcinoma[26]. However, only 65 per cent of colorectal cancers are associated with a blood CEA concentration of over 5 ng ml^{-1} at diagnosis, while 64 per cent of pancreatic cancers, 67 per cent of stomach cancers and 31 per cent of breast cancers are associated with a CEA concentration of over 5 ng ml^{-1} at diagnosis. Carbohydrate antigen (CA) 125 is another marker, the blood level of which is raised in 80 per cent of patients with ovarian carcinoma and normal in 99 per cent of healthy women. However, CA 125 is not entirely tumour specific as its concentration in blood is raised in 45 per cent of pancreatic cancers, 24 per cent of lung cancers, 17 per cent of colorectal cancers and 8 per cent of breast cancers[27,28]. While CEA and CA 125 are not tumour specific, a raised serum CA 125 level with a normal CEA level would be very suggestive of ovarian carcinoma. Differentiating ovarian ascites from non-ovarian malignant ascites is important from a therapeutic point of view (*Figs 1* and *2*) and so performing both CEA and CA 125 assays would be useful in women with malignant ascites of unknown origin. α-fetoprotein is a marker for hepatocellular carcinoma, but it is insensitive and has no role to play in the diagnosis of hepatocellular carcinoma as the diagnostic accuracy of ultrasonographic scan is far superior[29,30]. In summary, tumour markers are of little value in determining whether ascites is malignant in origin, but they may be useful in diagnosing the tumour of origin.

Radiology

Plain abdominal radiology is unreliable in the detection of ascites[31], although more modern imaging techniques are useful, especially ultrasonography, which is able to detect as little as 100 ml of fluid in the peritoneal cavity[31]. Computed tomography (CT) and magnetic resonance imaging (MRI) are also effective at detecting ascites; MRI has the advantage of being able to distinguish more clearly between fluid collections and surrounding normal tissue[32]. However, these latter two investigations are used less often than ultrasonography. Clinically unsuspected ascites is increasingly being diagnosed at imaging, especially in patients who undergo ultrasonography as an investigation for abdominal pain of unknown origin.

Imaging cannot distinguish between benign and malignant ascites but it may detect simultaneously the presence of solid tumour in the abdomen. Ultrasonography, CT and MRI all have good diagnostic accuracy in detecting liver metastases and other hepatic tumours[33,34], with CT and transvaginal ultrasonography providing reasonable accuracy in the diagnosis of ovarian carcinoma[35,36]. CT is also the most useful investigation in the diagnosis of pancreatic cancer[37]. While endoscopy is pre-eminent in the diagnosis of oesophageal, gastric and colorectal carcinomas, radiological imaging techniques are nevertheless good at visualizing these tumours, and have been used in tumour staging and patient follow-up[38]. Ascites detected by ultrasonography, CT or MRI, in the presence of typical imaging features of a malignant tumour, is strongly suggestive of a malignant cause for the ascites; this finding aids the clinician in deciding on the next investigation, e.g. to obtain histological or cytological proof, should this be considered necessary. Other radiological investigations, such as barium enema, which are unable to detect ascites, may be used to demonstrate the primary tumour when there is a direct clinical indication (*Table 2*).

Cytology

A positive cytology result confirms a malignant aetiology in ascites; in the right hands it has a specificity of 100 per cent[39–41]. Unfortunately, it is not very sensitive, with only about 60 per cent of malignant aspirates being cytologically positive[2,39]. If there is a high suspicion of malignancy on clinical or radiological grounds, repeat cytology should be performed. Runyon *et al.*[39] analysed ascitic fluid in 45 patients with malignancy-related ascites and correlated the findings to clinical and autopsy features. They subdivided their patients into five groups: peritoneal carcinomatosis without massive liver metastases; peritoneal carcinomatosis with massive liver metastases; massive liver metastases with no peritoneal carcinomatosis; hepatocellular carcinoma; and chylous ascites. Although they found 64 per cent of the total group had a positive cytology, 97 per cent of the patients in the two groups with peritoneal carcinomatosis had a positive or suspicious cytology, with cytology always negative in the other three groups (liver metastases alone, chylous ascites or hepatocellular carcinoma). Thus cytology is highly sensitive for peritoneal carcinomatosis.

Table 2 Diagnosis of ascites of unknown origin

Routine investigations	Remarks
Clinical history	
Clinical examination	
Blood tests	
Full blood count	
Liver function tests	
CEA and CA 125	Women only
Diagnostic paracentesis	
Cytology	Repeat if not malignant
Biochemistry	Total protein; others (see text)
Microbiology	Exclude infectious causes
Ultrasonography	
Abdomen	Confirm ascites, omental caking
Pelvis	Ovarian primary
Liver	Metastases, cirrhosis, hepatocellular carcinoma
Additional investigations to be performed when there is a specific clinical indication	
Computed tomography	
Barium enema/colonoscopy	
Gastroscopy	
Laparoscopy	
Laparotomy	

CEA, carcinoembryonic antigen; CA, carbohydrate antigen

Biochemical composition of ascites

Many biochemical parameters of ascitic fluid have been analysed in attempts to separate malignant from non-malignant ascites. Fibronectin, cholesterol, lactate dehydrogenase, sialic acid, serum–ascites albumin gradient, proteases and antiproteases have all been studied[25,40–44]; although sensitivities and specificities vary widely, ascitic fibronectin performs best in most series. However, further work is required before a single test can be used routinely to differentiate accurately between malignant and non-malignant ascites.

Laparoscopy

Diagnostic laparoscopy is a useful technique in patients for whom simple investigations have failed to determine the cause of ascites. In two reported series the correct diagnosis was obtained in 86–94 per cent of cases when laparoscopic observation and biopsy were combined[45,46]. The morbidity in these series, comprising 227 cases, was 6 per cent, prolonged leakage of ascites from the port site was the commonest complication, which led to bacterial peritonitis and death in two patients[46]. In a UK series, 25 patients had a diagnosis of intra-abdominal malignancy made at laparoscopy and in 21 of these the tumour of origin was identified[47]. This indicates that laparoscopy is useful in determining the primary tumour in cases of malignant ascites. Port site recurrence is a concern in laparoscopy for malignant disease[48]. Only three cases of port site metastases have been reported after laparoscopy for malignant ascites[49] and, given that laparoscopy under these circumstances is being performed for advanced disease, port site recurrence may not be a significant problem.

Established treatments for malignant ascites

There have been many different treatments advocated for malignant ascites, reflecting the inadequacy of most of them.

Symptomatic paracentesis

Symptomatic paracentesis is still the mainstay of treatment for patients with malignant ascites, giving good, although temporary, relief of symptoms related to the build-up of fluid in about 90 per cent of patients[50]. Although it can hardly be described as the 'gold standard', it is the method against which all new treatments must be compared.

In symptomatic patients it is generally safe to perform paracentesis 'blind', since there is a large volume of clinically detectable fluid. However, some patients have loculated ascites, large tumour masses, or adhesions secondary to intra-abdominal surgery or chemotherapy, and insertion of the trochar under ultrasonographic control is advisable in these patients[50]. Possible complications of paracentesis include secondary peritonitis, pulmonary emboli and hypotension[50]. One study reported two deaths from peritonitis and two from pulmonary emboli in 100 patients undergoing 127 paracenteses[51]. In a further study, 109 consecutive sonographically guided therapeutic paracenteses were performed on 43 patients with three complications of hypotension, fatal in two instances[50].

Fluid can be aspirated immediately, followed by removal of the cannula, or the cannula can be sutured in place and the fluid allowed to drain over a period of 12–72 h. The rapid removal of a large volume of ascites causes fluid shifts across compartments and leads to a reduction in effective circulating blood volume, and possible renal impairment and hyponatraemia[52]. It is necessary, therefore, to expand the intravascular compartment by intravenous infusion during paracentesis. Draining up to 10 litres of ascites per day has been shown to be safe provided intravenous colloid replacement is used as opposed to crystalloid[53]. The main problem with repeated paracentesis for malignant ascites is protein depletion. One study found that a group undergoing paracentesis alone had a significant drop in mean serum albumin level, from 32·5 g l^{-1} at diagnosis to 28·0 g l^{-1} after 1 month[54]. Another study found a drop in both protein and albumin concentrations in serum in a group receiving paracentesis only, from mean levels of 58·7 and 32·0 g l^{-1} respectively before treatment to 57·7 and 29·9 g l^{-1} respectively 6 weeks later[55].

In summary, therefore, symptomatic paracentesis with plasma volume expansion is effective in alleviating the symptoms of tense ascites but requires repeated hospital admissions, leads to protein depletion and exposes the patient to a small but significant risk of peritonitis.

Diuretic therapy

Diuretic therapy is the most useful single treatment in ascites secondary to cirrhosis, in which patients retain sodium and water as a result of the renin–angiotensin–aldosterone pathway[56]; spironolactone is the most effective agent. In malignant ascites, however, diuretics are generally considered ineffective, but this has not been well validated. One study quoted in support of this view examined the effect of frusemide and bumetanide in only 12 cases[57], and showed no beneficial effect. The only studies examining the effects of spironolactone in malignant ascites have actually shown a benefit, at least in selected patients. One found that 13 of 15 patients treated with increasing doses of spironolactone had a good response, with eight remaining free of ascites until death[24]. Plasma renin and aldosterone levels were measured in five of these patients, and renin levels were raised in all of them, while aldosterone levels were raised in only three. A further study of diuretics in malignant ascites was performed in 21 patients[25] divided into three groups: peritoneal carcinomatosis; chylous malignant ascites; and massive hepatic metastases. The three patients with massive hepatic metastases responded well to spironolactone, with mobilization of ascites and weight loss without complications, while the other patients had no response. The massive hepatic metastases group also had a raised serum renin concentration and high serum ascites–albumin gradient, although serum aldosterone levels were not raised. From these data the authors concluded that patients with massive hepatic metastases behave more like patients with cirrhotic ascites. Further work is needed to identify clearly which patients will benefit from diuretic therapy.

Systemic therapy

It is outside the scope of this article to review individual systemic treatments for each primary tumour. However, if a patient develops malignant ascites secondary to a primary tumour which is known to be responsive to systemic therapy, then such therapy should be instituted. For example, patients with ovarian carcinoma often develop ascites even in stage I and II disease[58]. In all these patients systemic chemotherapy is the mainstay of treatment after staging and debulking laparotomy. Median survivals for stage III and IV disease of up to 44 months can be achieved by appropriate combination chemotherapy, while 5-year survivals approaching 50 per cent can be achieved in stage I and II disease, even when ascites is present at diagnosis[59].

Intraperitoneal chemotherapy

Administering chemotherapeutic agents directly into the peritoneal cavity is a very attractive concept, as a local effect may be possible while avoiding the problems of generalized toxicity. Drugs administered into the peritoneal cavity are generally absorbed via the portal circulation and first pass metabolism by the liver allows high concentrations in the peritoneal cavity with low systemic concentrations, and therefore a low incidence of systemic side-effects[60]. One of the problems of intraperitoneal administration is inadequate distribution of the agent and the importance of instilling the agent in a large fluid volume has been demonstrated[61]; at least 2 litres are required to achieve a good distribution. Markman[62], in his review of intraperitoneal chemotherapy in ovarian carcinoma, concluded that the intraperitoneal route was useful but that the best agents have not yet been identified. Similarly Cunliffe and Sugarbaker[63] reviewed intraperitoneal chemotherapy in gastrointestinal malignancy. They argued for the use of immediate postoperative intraperitoneal chemotherapy on the basis that 74 per cent of patients with colorectal cancer who relapse after surgery develop recurrence either at the resection site or on peritoneal surfaces; immediate postoperative intraperitoneal chemotherapy should prevent viable cells spreading intra-abdominally. Furthermore, drug delivery in the immediate postoperative period is simple and cheap, and the increased postoperative morbidity is minimal[63].

Peroperative intraperitoneal chemotherapy has been used successfully in patients with gastric cancer with serosal involvement. It conferred a survival advantage in a study of 50 patients assigned randomly to either no treatment or intraperitoneal mitomycin absorbed on to activated charcoal[64]. However, a UK study of intraperitoneal cisplatin in patients with gastric cancer failed to detect any survival advantage compared with historical controls[65].

No large studies of intraperitoneal chemotherapy in patients with malignant ascites have been performed. The biggest available, from Appelqvist and colleagues[51], reported the results of intraperitoneal thiotepa in 23 patients with malignant ascites. There were symptoms of intestinal obstruction in five, with one consequent fatality. Autopsies showed abundant intestinal adhesions in 60 per cent of patients. This study highlights one of the main side-effects of intraperitoneal therapy. Other intraperitoneal chemotherapeutic agents are tolerated better, however, and small studies of both cisplatin[66] and bleomycin[67] have shown 50 per cent response rates in terms of resolution of ascites with minimal morbidity. Large randomized trials are required to determine whether intraperitoneal chemotherapy is any more effective than other forms of treatment.

Intraperitoneal radiocolloids

Radioactive colloids were first used in the treatment of malignant ascites in 1945[68]. Phosphorus-32 (^{32}P) has proved the most useful, since it is able to penetrate tissues to a depth of 8 mm and has the longest half-life (14 days). In 1966 Ariel and co-workers[7] reported that 78 of 145 patients (54 per cent) received some benefit from intraperitoneal ^{32}P. They also found that patients with small peritoneal seedlings were likely to respond while patients with large volumes of solid tumours were not. Similarly, Jackson and Blosser[6] reported an objective response in 81 of 200 (40 per cent) patients with malignant ascites.

^{32}P can give very effective palliation with no reaccumulation of ascites for over 6 months in some cases. However, most responses are more modest with repeat administrations being required. Side-effects in patients with ascites are minimal[6], but two recent articles reviewing the use of ^{32}P in patients with ovarian carcinoma without ascites described an incidence of small bowel obstruction of between 8 and 15 per cent[69,70]. No randomized comparative study has been performed and so no survival advantage has been demonstrated over any other form of treatment.

Peritoneovenous shunt

In 1974 Le Veen introduced the concept of a peritoneovenous shunt to treat patients with refractory ascites. The Denver shunt soon followed and it and the Le Veen shunt have been the most commonly used shunts ever since. Peritoneovenous shunts are able to provide effective palliation of symptoms in 64–77 per cent of cases of malignant ascites[54,71–73]. Failures are usually due to occlusion of the shunt, but no difference in patency has been demonstrated between the Denver and the Le Veen shunts used for malignant ascites[54,73], although there have been no randomized prospective trials. One such trial has been performed in patients with cirrhotic ascites: 12 patients randomized to receive the Le Veen shunt and ten to receive the Denver shunt. The Le Veen shunt had a superior patency and was recommended in preference to the Denver shunt[74].

Helzberg and Greenberger[71], in their review of 12 series incorporating 198 patients with peritoneal shunts for malignant ascites, described a complication rate of 25 per cent. The majority were due to shunt occlusion, with transient heart failure due to fluid overload being the next most common. Coagulopathy is another well recognized complication of shunt insertion, although it is much commoner in cirrhotic ascites than malignant ascites[75]. In one study a change in the coagulation measurements was found in all patients with a functioning shunt[73]. This has been borne out by others such that an increased concentration of fibrinogen degradation products is now regarded as an index of shunt function[73]. Other complications include tumour dissemination, pulmonary embolus and thrombosis of the superior vena cava. Qazi and Savlov[72] showed that tumour implants at the site of opening of the venous end of the shunt occurred in two of eight patients at autopsy, although widespread dissemination of tumour cells did not occur. Death attributed to tumour dissemination or embolus after shunt insertion has been reported in only six instances[76,77].

In summary, peritoneovenous shunt insertion can give effective palliation of ascites in about 70 per cent of selected cases. However, the procedure has an associated mortality, a high morbidity rate and a heavy cost in terms of time and money, as patients need to be monitored closely for at least 24 h after operation, with a central venous pressure line to monitor fluid balance and clotting screens to test for coagulation disorders. It is agreed by most authors that shunt insertion is contraindicated in patients with malignant ascites from a gastrointestinal origin, because of the universally poor prognosis. Furthermore, a shunt should only be used in non-gastrointestinal malignancies when other treatment options have failed and when the patient is considered likely to survive for more than 3 months[78] (*Figs 1–3*).

Novel treatments for malignant ascites

Immunotherapy (biological response modifiers)

Several biological response modifiers have been used in clinical trials. The most promising of these is OK-432, the Su-strain of *Streptococcus pyogenes* A3. When injected intraperitoneally into patients with malignant ascites OK-432 causes a rapid influx of neutrophils into the peritoneal cavity within 24 h of injection. This is followed 4–7 days later by a raised concentration of both macrophages and T lymphocytes in the ascitic fluid, with destruction of tumour cells and reduction of ascites[79]. In a large Japanese study of 200 patients with malignant ascites of gastrointestinal origin[55], 150 randomly selected patients were given six intraperitoneal injections of OK-432 at

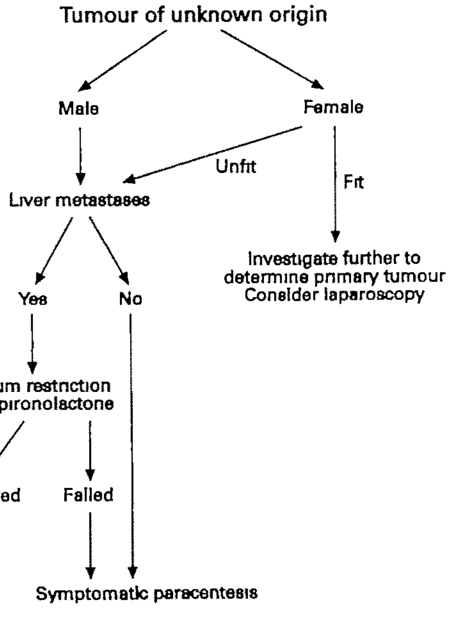
Tumour of unknown origin
Male
Female
Unfit
Fit
Liver metastases
Yes
No
Investigate further to determine primary tumour Consider laparoscopy
Sodium restriction and spironolactone
Resolved
Failed
Symptomatic paracentesis

Fig. 3 Treatment of malignant ascites of unknown origin

intervals of 1 week; the remaining 50 patients formed a control group. A complete response was defined as the inability to drain any fluid after the 6-week dosing period and a partial response was defined as a decrease in abdominal girth of 10 cm or more. Seventy-six patients had a complete response and eight had a partial response, giving a total response rate of 62·7 per cent. A survival advantage was also demonstrated with the OK-432 group surviving a mean of 10·2 months compared with 3·1 months for the control group. This impressive study has been followed up with smaller studies which have shown responses in approximately 50 per cent of cases[80,81]. The only study outside Japan reported a response rate in seven of 15 patients[82]. In summary, OK-432 looks promising as an agent for treating malignant ascites, especially resulting from gastrointestinal malignancy, but these results need to be validated further.

Radioimmunotherapy

Antibody therapy aimed at tumour-specific antigens has become an attractive possibility in the treatment of various types of malignant disease and malignant ascites is no exception. A phase I and II trial has been performed in 11 patients using a novel antimucin monoclonal antibody, 2G3, labelled with ^{131}I. Three of four patients treated with the highest dose showed temporary palliation, although histological studies showed preferential uptake by tumour, compared with normal tissue, in only two of five cases[83].

Matrix metalloproteinase inhibitors

Matrix metalloproteinases are a family of enzymes present within the normal healthy individual but produced in high concentrations by a variety of tumours, including colon, gastric and breast carcinomas[84–86]. These enzymes are thought to facilitate tumour invasion and metastasis by breakdown of the extracellular matrix, and this process is reversed by metalloproteinase inhibitors[87,88]. A synthetic inhibitor has been developed which has been shown to resolve ascites when given intraperitoneally to mice with malignant ascites secondary to an ovarian carcinoma xenograft; treatment is accompanied by an improvement in survival[89]. Similar results have been reported with a colorectal cell line[90].

The exact mechanism of action of the metalloproteinase inhibitors in ascites has not been established. It is known that the metalloproteinases, and gelatinase in particular, play an important role in tumour angiogenesis[91] as well as in tumour invasion. Inhibition of the metalloproteinases may exert an inhibitory effect on angiogenesis and vascular permeability or it may directly affect the tumour, preventing secretion of vascular permeability factors. There is good evidence that metalloproteinase inhibition leads to extracellular stroma formation around tumour cells, leading to necrosis of the tumour[89]. Phase I and II studies of intraperitoneal administration of Batimastat (British Biotech, Oxford, UK), a metalloproteinase inhibitor, in patients with ascites have been performed with encouraging results[92] (also G. Beattie *et al.*, unpublished results). Further studies are ongoing.

Conclusions

Malignant ascites is often the initial manifestation of disease which can present a diagnostic problem, both in terms of confirming malignancy and in defining the tumour of origin. The essential investigations, in addition to clinical history and examination, include diagnostic paracentesis for cytology, ultrasonography and blood tests (full blood count, liver function tests, and CEA and CA 125 estimations in women). A combination of these tests will confirm the diagnosis of malignant ascites in the vast majority of cases, as cytology should be positive in over 95 per cent of patients with peritoneal carcinomatosis[39] and, in the cytologically negative 'non-peritoneal carcinomatosis' group, ultrasonography will detect the majority of liver metastases and hepatocellular carcinomas[29,33].

Having confirmed a malignant cause, a search for the tumour of origin should generally be made, if this has not already been established. The results of the clinical evaluation performed thus far will guide the clinician towards the most appropriate investigations. In some patients, however, it is inappropriate to carry out extensive investigations to delineate the primary tumour because this knowledge will not affect management. This is particularly true for men with a positive cytology, for whom ultrasonography and blood tests have failed to reveal the tumour of origin. Conversely, women with a positive cytology should be investigated to the extent of laparoscopy or even laparotomy, unless they are considered to be too frail to undergo any form of treatment; patients with an ovarian primary can receive effective palliation for many months with debulking laparotomy and chemotherapy. *Table 2* lists appropriate investigations for the diagnosis of malignant ascites.

New approaches may result in treatment for malignant ascites changing over the next few years. However, at present, treatment regimens must rely on conventional therapy. Several suggested regimens have been proposed previously[25,76,78] but none is based on a knowledge of the tumour of origin. Malignant ascites is a heterogeneous condition dependent upon the tumour of origin and treatment should be planned with a knowledge of the primary tumour if at all possible (*Figs 1–3*). The fit patient with ovarian ascites will undergo a very different treatment regimen from the patient with a gastrointestinal primary.

The approach outlined above will, the authors believe, allow the best possible palliation of symptoms within the limitations of conventional therapy and with minimum morbidity. The poor overall survival of patients with malignant ascites should not lead us to forget that palliation is of the utmost importance to those in their final months of life.

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operation, or after a clearance thought by both to be complete. It can occur in the presence or absence of disseminated disease. When reporting results, these circumstances should be stated.

Preoperative locoregional staging

For practical purposes, preoperative locoregional staging will identify two broad groups of tumour: locally not extensive and locally extensive. These are related to the cancer-specific endpoints of local recurrence and survival. The former includes tumours confined to the bowel wall and those that have penetrated beyond to a 'slight' degree. Survival is high and local recurrence low. There is no accepted agreement among pathologists as to how far into the extrarectal tissues this should be in measured distance, but less than 5 mm has been suggested. Tumours that have penetrated into the extrarectal tissues by more than this would then be locally extensive. Here survival is low and local recurrence high[4]. These two groups can be recognized before operation by a combination of digital examination, ultrasonography, CT and MRI in 80 per cent or more of cases[19,20]. They cut across the conventions of pathological staging and have the greatest prognostic resolution of any clinicopathological subdivision of rectal cancer.

Essentially the two groups represent a subdivision of stage T_3 (equivalent to Dukes B or Astler Coller B_2). The locally not extensive tumour includes the pathological stages T_1, T_2 and less extensive T_3 (in the Dukes classification A and less extensive B). Five-year survival is high (over 70 per cent) and local recurrence low (less than 5 per cent). In contrast, the locally extensive tumour involves pathological stages of more extensive T_3 and T_4 or with Dukes the extensive B tumour. Here 5-year survival is low (about 30 per cent) and local recurrence high (10–30 per cent)[4]. No conventional staging system results in such a difference in cancer-specific endpoints. Informally, most surgeons make this subdivision in their preoperative assessment.

Preoperative determination of lymph node status is so inaccurate as to be almost useless. Imaging, including CT and ultrasonography, can detect enlarged nodes, as can digital examination, but sensitivity and specificity are poor for tumour involvement. About 30 per cent of metastatic nodes are 5 mm or less in size[21]. At present there are no means of assessing the mesorectum preoperatively for tumour rests. Preoperative locoregional staging comes down, therefore, to the assessment of level and local extent. Each may indicate the likelihood of regional lymphadenopathy, including those nodes on the lateral pelvic wall, by inference.

Choice of treatment

Radiotherapy

A discussion of radiotherapy would require a detailed article in its own right. As a brief summary, randomized controlled trials have shown that, when used preoperatively as an adjuvant to 'curative' surgery, radiotherapy can reduce or delay local treatment failure[22–24]. Preoperative appears more effective than postoperative radiotherapy. Published randomized prospective trials of postoperative radiotherapy have been disappointing; morbidity is higher[25,26]. Postoperative radiotherapy can damage the colonic segment brought down to an anastomosis and is more likely to cause small bowel enteropathy. These are important considerations with regard to future function and surgeons should take them into account when planning treatment. Whether used before or after operation, a technique employing multiple ports, concentrating a high dose on the tumour, is less likely to cause damage than those using a larger field.

Radiotherapy given before operation can render operable a locally extensive tumour of dubious initial operability, offering good local control after surgery in many cases[27]. For locally extensive tumours when operability is not in doubt, preoperative radiotherapy will reduce the chance of local recurrence. Patients with such lesions are certainly the most appropriate for entry into prospective randomized trials of preoperative radiotherapy, but there are now enough data to indicate that it should be given routinely in such cases. Radiotherapy for non-extensive tumours is inappropriate, since local recurrence rates after surgery alone are low, and radiotherapy is not without long-term adverse effects.

Advocates of a purely surgical solution to low rectal carcinoma maintain that local recurrence is due to inadequate surgery, citing the main weakness of multicentre trials to be the unknown variable of surgical technique. Radiotherapy, it is maintained, should not be used to make up for defective surgery and there is undoubtedly a surgeon-related variable in local recurrence[14,28]. It is known, however, that 5–10 per cent of tumours can be so extensive locally as to be inoperable or of dubious operability and that when the tumour is sited in the lower rectum, pelvic wall lymphadenopathy is quite possible. There is no standard operation for rectal cancer which will remove this potential source of local treatment failure.

The available evidence demonstrates that radiotherapy can be effective in shifting the dividing line between a palliative or curative local removal. It can also reduce local recurrence in the less advanced case. Perhaps its effect is by sterilization of tumour metastases in lateral pelvic wall nodes. Radiotherapy, therefore, may be achieving what the supporters of lateral pelvic lymphadenectomy seek, without the local morbidity caused by the surgery.

Surgery

The basic principles of surgery are no different whether or not radiotherapy is given in conjunction. There are three requirements: adequate locoregional clearance, minimal complications and satisfactory function. Of these, the first is by far the most important, since local recurrence results in death from the tumour in well over 90 per cent of patients who develop it[29]. Surgery is the mainstay of treatment.

Sphincter preservation. There are two surgical options relating to rectal cancer: total anorectal excision or a sphincter-saving procedure. With improvements in anastomotic technique, anterior resection has been applied increasingly to cancers lower in the rectum and is now the operation of choice in the majority of cases.

A few patients are amenable to local excision, but they comprise only 5 per cent of the total and must be selected very carefully. Endorectal ultrasonography is an essential adjunct to digital examination; their accuracies in assessing penetration of the rectal wall are approximately

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Review

Treatment of non-disseminated cancer of the lower rectum

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Apart from the occasional tumour which is suitable for local excision, most low rectal cancers are best treated by anterior resection with complete removal of the rectum; the construction of a coloanal reservoir should allow routine sphincter saving. This surgery may be carried out independently of adjuvant radiotherapy which, if given, should be administered before operation.

Surgery and radiotherapy are both regional treatments for non-disseminated cancer of the lower rectum and there is now general agreement that local treatment failure is the correct endpoint to judge their effectiveness. Local recurrence is influenced by the pathology of the tumour but is also related to surgical technique and can be reduced by radiotherapy. Neither modality affects distant failure.

The choice of treatment is determined by the clinical stage of the tumour. Preoperative staging is an attempt to estimate the pathological extent of the tumour before surgery. At the locoregional level this means the anticipation as accurately as possible of the pathological stage that will be reported by the pathologist on examining the excised specimen. This is done by digital palpation of the tumour and imaging, including pelvic and endoluminal ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI).

Histopathology

Historically the choice of treatment has been based on histopathological criteria and it continues to be so. When sphincter-preserving operations were described at the end of the 19th century, it was the pathological studies of Miles[1] on lymphatic involvement that turned opinion away from these and led to abdominoperineal excision becoming the operation of choice. So it remained until pathologists reported the limited degree of intramural spread distal to the lower border of the tumour[2,3]. Gradually the pendulum swung back towards sphincter preservation. The application of anterior resection has since been extended in the light of further pathological studies on the distal margin.

The classic paper of Dukes and Bussey[4] on the influence of direct local spread of rectal carcinoma on local recurrence lay in obscurity for 20 years or so. Subsequent analysis of risk factors for local recurrence has shown this variable to be of prime importance[5]. The association between lateral margin involvement and local recurrence reported[6] is largely a refinement of their studies, which can be summarized along the lines that if the tumour is not completely removed circumferentially, then it is very likely to recur. This circumstance could be due to local extensiveness or inadequate surgery.

Another recent observation is the pathological demonstration of tumour rests within the mesorectum distal to the level of its lower border[7]. The prevalence of this occurrence is not known accurately. It has been suggested that this is an important source of local recurrence which, it is maintained, can be reduced to a very low level by carrying out total mesorectal excision during anterior resection. While this technique may optimize the capability of anterior resection to reduce local recurrence, it cannot be the whole story.

Local recurrence occurs after total rectal excision in which the entire mesorectum is removed[8,9]. Either the operation is being done inadequately or there must be another explanation. This is forthcoming through the demonstration of metastases in the nodes located on the lateral pelvic wall associated with the internal iliac vessels[10–12]. These have been proven histopathologically to harbour tumour in up to 30 per cent of patients undergoing major surgery for rectal cancer[12]. The observation may explain the higher local recurrence rates for tumours in the lower compared with the upper rectum after surgical treatment[13]. There is also a relationship between the presence of lateral pelvic lymphadenopathy and nodal involvement within the mesorectum[12]; the latter is an indication of the presence of the former. The lateral pelvic nodes are not removed by any standard major operation for rectal cancer.

The histological grade of the tumour is also related to local recurrence. Poorly differentiated growths have a higher incidence of locoregional recurrence than well or moderately differentiated tumours[14]. Distal intramural spread, greater than 1 cm below the lower border of the tumour, is almost always associated with poor differentiation[15,16]. There is good agreement among pathologists in grading poorly differentiated tumours in the resected specimen[17] but the error in identifying these in preoperative biopsy specimens is as high as 50 per cent. Thus the preoperative biopsy with a high sensitivity but low specificity is only of limited use.

In a recent article, Marsh *et al.*[18] have shown that it is possible to obtain different local recurrence rates within the same population of patients using different definitions for local recurrence and different clinicopathological subgroups as denominator. There is, indeed, no generally accepted standard definition. This poses a difficulty when attempting to compare one report with another. Recurrence within the field of removal of the primary tumour can occur after an incomplete clearance known to surgeon or pathologist at the time of the original

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95 and 80 per cent respectively[19,20,30]. Tumours suitable for local excision must be accessible, small and confined to the rectal wall; they should not show anaplastic histology[31]. Modern technology affording access to the upper rectum, e.g. transanal endoscopic microsurgery[32], may increase the scope of local excision, but the rules of case selection based on the local pathology must still apply.

Many studies have shown that if a margin of 2·5 cm of normal rectum below the distal border of the tumour is achieved by anterior resection, there is no compromise of survival or local clearance compared with those of abdominoperineal excision[8,14,16,33]. This means that most tumours 6 cm or more from the anal verge, therefore within 2 or 3 cm above the anorectal junction, are suitable for restorative resection.

Much of the argument concerning the incidence of local recurrence after surgery now centres around lateral clearance[6] and mesorectal excision[7]. These have been considered already from the pathological point of view and the arguments are directly translatable to clinical practice given the pathological basis of surgical treatment. Local recurrence may well be influenced by inadequate surgery[14,28], but pathological studies summarized above show unequivocally that some tumours will have extended beyond the scope of adequate local clearance, however good the surgeon. In this circumstance, neither total rectal excision nor anterior resection can avoid local recurrence completely. The possibility of lateral pelvic node involvement must be a major factor here, given the unequivocal evidence of its occurrence. Lateral pelvic lymphadenectomy has a high morbidity, including pelvic nerve damage. There are no controlled trials of its effectiveness. Some non-randomized comparative studies have suggested benefits[34] in terms of local recurrence and survival; others have not[35].

In view of the inaccuracy of preoperative assessment of regional lymphadenopathy, the choice between anterior resection and total anorectal excision depends largely on distal margin of clearance and degree of local penetration. Both these factors can be determined before operation. Clearly, sphincter function must be adequate for a restorative procedure. Based on these criteria, anterior resection is now offered to most patients with cancer of the middle or lower third of the rectum. This may not, however, be the optimal operation for growths at this level in most surgeons' hands. The standard anterior resection does not remove the entire mesorectum. While complete mesorectal clearance does not abolish local recurrence (see above), it will minimize it; it will optimize the capability of anterior resection to achieve local tumour clearance. There is, therefore, a strong oncological argument for adopting anterior resection with complete rectal (and therefore mesorectal) excision as the standard operation for low rectal cancer when sphincter preservation is justified.

Complete removal of the rectum requires a coloanal anastomosis as the routine means of reconstruction. Its morbidity is little different from a low colorectal anastomosis[36,37] and the techniques available are now standard. The indication for a temporary stoma is the same for both procedures. There may, however, be a problem with function, since this is related to the level of the anastomosis which determines the amount of remaining rectal reservoir capacity[38]. It may take 6–12 months for frequency, urgency and urge incontinence to settle after low colorectal or 'straight' coloanal anastomosis[39]. This difficult period is a significant fraction of the patient's life expectancy among the 40 per cent or more who are destined to die from disseminated disease within 3 years after a 'curative' resection.

It is now clear from non-randomized and randomized studies that adding capacity in the form of a colonic reservoir to a coloanal reconstruction can abolish or substantially reduce dysfunction, greatly improving quality of life[40–43]. Technically, it is simple to make the reservoir, and the anastomosis is no more difficult than that of straight coloanal reconstruction. As with the ileoanal reservoir, frequency is inversely related to capacitance of the neorectum, and capacitance also diminishes urgency and improves continence[40–43]. Some patients may, however, develop difficulty with evacuation and it is important to use no more than 12–16 cm of colon for the two-loop construction. The addition of a reservoir improves quality of life without increasing the technical complexity of the procedure.

With the exception of the small group of tumours suitable for local excision, the evidence available at present supports the view that anterior resection with complete rectal removal and coloanal reservoir reconstruction should be the routine sphincter-saving operation for low rectal cancer. This can be carried out independently of any adjuvant radiotherapy provided the radiotherapy is given before surgery, which now appears to be preferable to postoperative treatment. This approach gives the patient the best cancer-specific and functional outcome of any major restorative resection.

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Review

Phlegmasia caerulea dolens and venous gangrene

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Phlegmasia caerulea dolens and venous gangrene are rare conditions that tend to occur in association with malignancy. They are characterized by total or near-total occlusion of the venous drainage of the limb, including the microvascular collaterals. Associated mortality and morbidity rates are high, especially when progression to venous gangrene has occurred. Treatment options are limited; elevation and anticoagulation are recommended as first-line management. Experience with thrombolysis has been disappointing although intra-arterial administration of thrombolytic agents may improve results. Thrombectomy cannot be advocated routinely. Little advance in management, or in life and limb salvage, has been made in the past 30 years.

Phlegmasia caerulea dolens (PCD) and venous gangrene are related clinical entities that arise due to acute massive thrombosis of the venous drainage of an extremity. While these venous disorders are rare, it is difficult to compute an exact incidence for PCD or venous gangrene. A spectrum of disorder exists, ranging from mild calf vein thrombosis through iliofemoral deep vein thrombosis to the severe conditions of PCD and venous gangrene which are threatening to both life and limb. The first description of PCD is attributed to Fabricius Hildanus[1] in the sixteenth century, and the term was first used in 1938 by Grégoire[2] to distinguish this ischaemic form of venous thrombosis from the more common non-ischaemic entity, then called phlegmasia alba dolens. PCD is characterized by limb swelling, cyanosis and pain. It represents a reversible phase of ischaemic venous occlusion that may progress to venous gangrene in 40–60 per cent of cases[3,4]. Venous gangrene is always preceded by PCD[5], starting distally and spreading proximally. Gangrene may involve skin and subcutaneous tissue, or muscle, or both, and so may threaten limb viability.

Pathophysiology

The fundamental process that occurs in PCD and venous gangrene is total or near-total thrombotic occlusion of venous drainage, including the microvascular collaterals. Single or multiple obstructions to the main veins of a limb have not been shown to produce any important obstruction to the venous circulation[6]. In dogs, only division of all the veins at the root of the hind limb leads to changes consistent with those seen in venous gangrene[7]. PCD is characterized by patency of a number of major or collateral veins at the root of an extremity, which accounts for the potential reversibility of the ischaemia. In venous gangrene there is complete obstruction to the venous outflow from the limb.

Obstruction to venous outflow leads to changes in the forces that govern influx and outflow of fluid at both the arterial and venous end of the capillary. Under the normal Starling equilibrium[8], hydrostatic pressure drives fluid out of the capillary into the interstitium at the arterial end and fluid is reabsorbed at the venous end where colloid oncotic pressure exceeds hydrostatic pressure. When the venous outflow is occluded, hydrostatic pressure at the venous end of the capillary rises to exceed colloid oncotic pressure and interstitial oedema develops. The increase in venous pressure may reach 16 to 17 times the normal value within 6 h of occlusion[9]. The development of oedema produces interstitial tissue pressures of 25–48 mmHg (normal pressure 0–10 mmHg) within 1–2 days[3,9,10]. Shock develops as a consequence of loss of plasma. Experimentally, large volumes of fluid have been shown to be lost into the affected limb[11]. Fluid loss into the interstitial spaces as great as 6–10 litres has been reported within 5–10 days of the onset of venous thrombosis[12].

There is debate over the mechanism of arterial insufficiency associated with PCD. A few case reports have described occlusive thrombosis of small peripheral arterioles[13] in venous gangrene, but others have confirmed arterial patency by angiography and anatomical dissection at autopsy. Consequently, spasm has been mooted, although there is no supporting evidence for this theory. Periarterial sympathectomy and acetylcholine fail to produce any improvement in tissue perfusion[2]. Neither decrease in blood flow[10,14] nor change in arterial pulse amplitude suggestive of spasm[10] has been demonstrated following experimental venous ligation and massive venous occlusion. It therefore seems likely that ischaemia results from collapse of small arteries when critical closing pressure is exceeded. Under normal conditions arteries remain open due to an equilibrium between pressure and tension in the vessel wall[15]. Tissue pressure is close to zero and has little effect on transmural pressure. Once hydrostatic pressure in the vessel falls below a critical point, tension in the wall will cause collapse of the vessel. In PCD and venous gangrene, hydrostatic pressure falls due to hypotension and tissue pressure increases due to oedema. If hydrostatic pressure falls to 50 mmHg and tissue pressure rises to 40 mmHg, arterial wall tension can overcome the transmural pressure of 10 mmHg, causing the vessel to collapse[10].

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Aetiology

A relationship between malignancy and thromboembolic disorders has long been recognized[16] and an underlying malignancy may be present in 20–40 per cent of patients[3,17,18]. True venous gangrene most often occurs in association with some form of malignant disease[18–21]. Often the tumour has not previously been detected[22]. Abnormalities of blood coagulation have been found in up to 95 per cent of patients with cancer, although clinically apparent thrombosis occurs in only 5–15 per cent[23,24]. In many instances where there is no apparent cause for thrombosis an underlying primary hypercoagulable state is found, such as intrinsic deficiencies of antithrombin III, proteins C or S, or plasminogen[25,26]. Lupus anticoagulant may be detected[27]. Recently, resistance to activated protein C has been demonstrated as a hereditary genetic defect that is frequently found in patients with recurrent venous thromboembolism[28,29]. Patients should be investigated for the presence of all these hypercoagulable states. PCD or venous gangrene may also occur in the following situations: after surgery or trauma, postpartum, in patients with a history of deep vein thrombosis, and in association with a variety of inflammatory conditions such as ulcerative colitis[30], pneumonitis and gastroenteritis[3]. Prolonged immobility is a precipitating factor. PCD and venous gangrene have been reported as complications of severe mitral stenosis with heart failure[31], after insertion of a vena cava filter[32], and following intravenous drug abuse[33]. In approximately 10 per cent of cases no cause is found[3,17,19].

Clinical features

Ischaemic venous thrombosis has been reported in patients ranging in age from 6 months to 87 years[17]. The highest incidence occurs in the fifth and sixth decades[18]. Women are affected more often than men[3] in a ratio of 4:3. In the lower limb the left side is affected more often than the right[17,18]. This is believed to be the result of compression of the left iliac vein by the overlying right iliac artery[34]. Symptoms of PCD are preceded by those of the commoner, non-ischaemic form of phlebothrombosis, phlegmasia alba dolens, in 50–60 per cent of cases[3,18]. Speed of onset is variable. Some cases are fulminant and can stimulate arterial occlusion, while others are more indolent and progress gradually from simple iliofemoral deep venous thrombosis to massive venous occlusion.

PCD is characterized clinically by the feature triad of swelling, pain and cyanosis; diagnosis is initially made on clinical grounds. Massive oedema develops rapidly, and the involved limb has a tense and firm quality. In a few instances oedema may extend to the trunk. Sequestration of plasma in the limb may be so intense as to produce cutaneous blebs or bullae. Pain is a constant feature and may begin over the femoral triangle, but it rapidly spreads to affect the whole limb. The pain is agonizing with a bursting quality, and may be difficult to control. Cyanosis is a striking feature, beginning distally, where it remains most intense, but spreading to involve the entire limb. Varying degrees of arterial hypotension, from mild to severe shock, have been reported in patients with PCD[35]. Arterial insufficiency may develop rapidly and arterial pulses diminish or disappear; excessive oedema may make palpation of pulses difficult and pedal pulses are palpable in only 17 per cent of patients. The femoral pulse is often weak and is absent in 9 per cent of patients[3].

Venous gangrene develops in 40–60 per cent of patients with PCD[3,4]. Gangrene starts distally and progresses proximally; it usually occurs within 2 days of the development of arterial insufficiency, although in some cases it has occurred within hours of the loss of pulses. Superficial gangrene accounts for 10–20 per cent of cases of venous gangrene. In this state arterial pulses are usually present, in contrast to deep gangrene involving muscle when pulses are usually absent[3,18].

The reported incidence of pulmonary embolism varies from 12 per cent[36] to 40 per cent[5,37] and the incidence is increased when tissue necrosis is present. In a series in which only patients with clinical, radiological and electrocardiographic evidence of pulmonary embolism were included, the incidence was 20 per cent[3].

Involvement of the upper limb is rare. Haimovici[18] reported arm involvement in only 4 per cent of patients with PCD, in contrast to venous gangrene which was associated with a 19 per cent incidence of upper limb thrombosis. Patients with upper limb ischaemic venous thrombosis usually have at least two of the following three features: (1) haemodynamic compromise due to poor cardiac output; (2) thrombosis of central veins (subclavian or axillary), often due to intravenous central venous catheters; (3) occlusion of peripheral veins[38]. Treatment and outcome are similar to those for the lower limb.

Contrast venography, which has been widely used to confirm the diagnosis and assess the extent of venous thrombosis, is generally regarded as the 'gold standard' investigation. However, venography may not be technically possible and is uninterpretable in 20–25 per cent of patients[39,40]. It is invasive, costly, and precipitates thrombosis in 2–3 per cent of normal cases[41]. Complete occlusion results in non-visualization of the deep venous system, and ascending venography is therefore of little diagnostic value in the assessment of PCD. In contrast to ascending venography, descending venography provides improved images of the iliocaval system. However, it is almost always impossible to obtain descending venograms via the ipsilateral femoral vein. Although descending venography may be possible via the contralateral femoral vein, involvement of the inferior vena cava frequently prevents this; descending venography via the upper limb is then the technique of choice.

Non-invasive assessment of thrombosis using continuous-wave or duplex Doppler ultrasonography provides a rapid and accurate method of assessment[42,43]. A review of studies assessing duplex ultrasonography against contrast venography in the diagnosis of proximal deep venous thrombosis reported a sensitivity of 93 per cent and specificity of 98 per cent for ultrasonography[44]. Ultrasonographic methods can be used at the bedside, avoiding transfer of severely ill patients to the radiology department.

Treatment

Many treatments have been advocated for PCD and venous gangrene, including sympathectomy, hot packs, sympatholytics, antivasospastic drugs, phenylbutazone, hyaluronidase, fibrinolysin and steroids, all to little effect. Some consider PCD as representing a terminal event in which efforts at therapeutic intervention are futile. Following progression of PCD to venous gangrene, therapeutic intervention is even less likely to be successful. Treatment is aimed at preventing propagation of thrombus and reducing venous hypertension, so preserving tissue viability. Initial management involves correction of hypotension by intravenous administration of fluids to improve tissue perfusion as far as possible. Bed rest and elevation of the affected limb in PCD encourages venous drainage through venous channels that remain patent; elevation is an important aspect of early management. The leg must be elevated high in the air, not merely laid on a pillow. Large foam wedges may be used, or the affected limb may be suspended from a high frame at the foot of the bed in the manner of gallows traction. Failure to achieve adequate elevation may account for progression to venous gangrene.

Definitive management thereafter involves three forms of treatment: anticoagulation, thrombectomy or thrombolysis, in any combination. Anticoagulation, fluid resuscitation and adequate elevation allow successful treatment in a significant proportion of patients with PCD[4,45]. An immediate intravenous bolus dose of heparin, 10 000–15 000 units, is recommended, followed by a continuous infusion to maintain the activated partial thromboplastin time at twice the control value[45]. If symptoms fail to resolve by 6–12 h, additional measures such as thrombolysis or thrombectomy are required. A marked contrast is seen in response to treatment between patients with uncomplicated PCD and those with venous gangrene. The combined results for cases reported from 1967 to 1985 (38 patients with 45 affected lower limbs) suggest that heparin is beneficial in all cases of uncomplicated PCD and in none of venous gangrene[4]. Heparin should remain the initial treatment of choice for uncomplicated PCD as it requires only intravenous cannulation and has fewer side-effects than thrombolysis. However, heparin-induced thrombocytopenia can develop, which requires coumarin anticoagulation to be substituted for heparin.

The first thrombectomy for PCD was performed by Leriche and Geisendorf[46] in 1939. This operation has been recommended as both a first-line and a secondary treatment following failure of anticoagulation[47]. Thrombectomy was enthusiastically advocated in the 1960s as the most logical treatment of PCD. It removes the massive venous occlusion at the root of the extremity that is the fundamental underlying cause of the condition. Thrombectomy is aimed also at preventing propagation of the thrombosis and subsequent gangrene, preventing pulmonary embolism, and avoiding serious postphlebitic sequelae. Early descriptions of thrombectomy for simple iliofemoral thrombosis claimed an 85 per cent patency rate if done within 10 days of the onset of thrombosis and reported normal legs with minimal or no oedema in 81 per cent of survivors[48]. However, higher rates of rethrombosis have been reported in thrombectomy for PCD[49]. A 5-year follow-up in patients with good early results discovered 94 per cent with significant oedema and stasis still requiring compression stockings[50]. Two-thirds of postoperative deaths resulted from pulmonary embolism[50]. While thrombectomy offers a treatment that can provide rapid relief of venous and compartmental hypertension[51], patients may be too ill to undergo general anaesthesia for the procedure. Thrombectomy fails to clear thrombus distally from small venous channels and consequently yields poor results in patients with venous gangrene[4,18]. It does not prevent future venous stasis due to valvular incompetence. For these reasons thrombectomy is now recommended only for patients in whom anticoagulation therapy has failed or is contraindicated, or for those with impending venous gangrene[4]. Thrombectomy combined with adjunctive regional thrombolysis may improve results[52]. Fasciotomy has been used alone or in conjunction with thrombectomy in a small number of patients[37,53], with indifferent results[4]. Theoretically it offers advantages in reducing compartmental pressures, but prolonged wound healing and risk of infection have prevented the technique playing much part in the treatment of PCD or venous gangrene.

Thrombolysis offers an attractive alternative method of treatment for both PCD and venous gangrene. Thrombolytic agents can be delivered into the occluding thrombus, allowing lysis in both major veins and smaller venous channels inaccessible to surgery, while preserving patency of existing venous collateral pathways. These potential advantages may be outweighed by contraindications to thrombolysis. When strict inclusion criteria were applied for treatment of uncomplicated deep venous thrombosis by thrombolysis, only 7 per cent of 209 patients had no contraindication to the use of lytic agents[54]. Descriptions of the use of thrombolysis as first-line treatment for PCD and venous gangrene are largely confined to individual case reports using streptokinase administered systemically[55], or urokinase delivered via transvenous catheters into the affected limb[56]. Successful resolution of symptoms is described but it is difficult to draw any wider conclusions. Thrombolysis has more frequently been used as a secondary measure following failure of anticoagulation. Weaver *et al.*[4] published results of one centre's experience with PCD (16 patients and 17 limbs), combined with the results of 12 further literature reports involving 38 patients and 45 limbs. Good results (two of two limbs), defined as survival without major amputation, were noted in the treatment of uncomplicated PCD with thrombolysis following failure of anticoagulation. In venous gangrene, thrombolytic treatment was less successful (three of five limbs)[4]. Heparin anticoagulation alone was successful in 12 of 12 limbs with uncomplicated PCD, but failed in all 12 limbs with venous gangrene. Thrombectomy was successful in 11 of 12 limbs with PCD, but gave poor results in venous gangrene, with failure in six of nine limbs treated. The remaining limbs either received unspecified anticoagulation or no treatment. These results are reflected in a later series from the same centre, but again the numbers involved were small[45]. Thrombolytic treatment for uncomplicated deep venous thrombosis produces poorer clearance of occluding than of non-occluding thrombosis; only 14 per cent of occluded segments had 50–100 per cent lysis[57].

Use of low-dose intra-arterial thrombolysis has recently been reported as an alternative to intravenous treatment[58]. Patients with PCD usually have systemic hypotension and a compromised circulation through the affected limb; this reduces the effective dose of lytic agent reaching the capillary system when delivered intravenously as systemic thrombolysis. Intra-arterial thrombolysis delivers the lytic agent to the capillary system and peripheral veins where it is most needed, and tissue plasminogen activator has proven successful in three patients[58].

The risk of pulmonary embolus in PCD is high and this may be increased by thrombolysis. Lysis may cause clot fragmentation[59] and manipulation of venous catheters may dislodge thrombus. The placement of a permanent or removable vena cava filter has, therefore, been advocated

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before starting thrombolysis[56,58]. Further indications for vena cava filters include contraindication to anticoagulation, inadequate thrombectomy and post-traumatic PCD[60].

Prognosis

PCD and venous gangrene remain life- and limb-threatening conditions. In the presence of an underlying malignancy or concomitant disease, response is poor to the severe physiological disturbance of massive thrombosis. The mortality rate is reported as 20–40 per cent[3,4,17,37].

Amputation for PCD and venous gangrene is necessary in 20–50 per cent of patients[3,18,61]. However, there is conflicting evidence about the extent of amputation required. Brockman and Vasko[3] found that tissue loss was so severe that 43 (61 per cent) of 71 patients undergoing amputation required an above-knee and 17 per cent a below-knee procedure. Haimovici[18], however, stressed the fact that many of the lesions of venous gangrene are superficial, in contrast to the deep tissue necrosis of pure arterial ischaemia. He reported that 60 per cent of survivors of venous gangrene required only minor amputation (toes, fingers or transmetatarsal) or debridement and skin grafting[18]. The mortality rate among amputees was 22 per cent overall, and 68 per cent in those who underwent above-knee amputation[18]. Timing of amputation for venous gangrene differs markedly to that for arterial disease. In arterial disease deep tissues are invariably compromised and delay in interventional treatment or amputation results in myonecrosis with systemic consequences. Amputation in venous gangrene should be delayed as long as possible while aggressive treatment is pursued to allow venous channels to open, limb swelling to subside and the extent of tissue loss to be established. Allowing swelling to reduce prevents the serious wound problems that arise following amputation of a grossly swollen limb. If amputation is delayed, all that may be required is superficial debridement or minor resection, which should be as conservative as possible[18].

Information on postphlebitic sequelae in PCD and venous gangrene is limited; their extent has not been formally evaluated. In published series to 1965, 102 (36·6 per cent) of 279 patients reported some form of postphlebitic problem, ranging from mild oedema to full-blown postphlebitic limb. This undoubtedly underestimates the full impact of PCD, as the majority of reports make no comment on this complication while others describe long-term sequelae in 60 per cent of patients[62].

Conclusions

PCD and venous gangrene are rare conditions and so the individual surgeon encounters them only a few times in a career. This situation accounts for the disparate nature of the accumulated literature on the subject, and the lack of long-term follow-up and consensus on best treatment. Lack of information on thrombolysis in the treatment of PCD and venous gangrene is disappointing, given its theoretical benefits. The wealth of experience of the use of thrombolysis for arterial thrombosis has not been fully exploited in venous disease due to the relative rarity of the latter. Intra-arterial thrombolysis represents an encouraging development among the treatment options and merits further research.

What remains certain is that morality and morbidity rates are high, and the threat to life and limb is considerably greater in patients with venous gangrene than in those with PCD. Treatment of the reversible phase of venous ischaemia in PCD offers a greater chance of success whether by anticoagulation, thrombectomy or thrombolysis. When venous gangrene occurs, the results of treatment are universally dismal and amputation rates high. Indeed, amputation may offer the only option if the patient is to survive. Choice of management and extent of treatment have to be carefully balanced in the one-third of patients with venous gangrene who have an underlying malignancy.

The best management for PCD is elevation, fluid resuscitation and anticoagulation with heparin, but further experience with thrombolysis may prove this to be the best first-line management. Currently, thrombolysis and thrombectomy are generally reserved for treatment following failure of anticoagulation or impending venous gangrene.

PCD and venous gangrene represent as serious a threat to life and limb now as they did 30 years ago. Treatment options have remained largely unchanged, unproven or only moderately successful.

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Growth enhancement of implanted human colorectal cancer cells by the addition of fibroblasts *in vivo*

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The effect of fibroblasts on the growth of HT29 human colorectal cancer cells was used to study stromal modulation of tumour growth dynamics. Fibroblasts were isolated from rat livers 1, 2·5 and 4 days after two-thirds partial hepatectomy and from normal livers. Cells harvested 2·5 and 4 days after hepatectomy ('fast' fibroblasts) had a significantly faster growth rate *in vitro* than those harvested on day 1 or those from normal livers ($P<0\cdot02$). The fibroblasts were inoculated with HT29 colorectal cancer cells into nude mice. Controls received cancer cells with or without a fibroblast cell line (C3H10T 1/2). At 3 weeks both tumour take and growth (size) were significantly greater in the group inoculated with cancer cells and 'fast' fibroblasts than in the other groups (tumour take 100 *versus* 42–75 per cent, $P<0\cdot03$; median tumour size 3·5 *versus* 0·3–0·4 g, $P<0\cdot02$). In conclusion, tumour growth is enhanced by fibroblasts, especially by those derived from actively regenerating liver. It is suggested that the stimulation is not only mechanical but may also involve a humoral mechanism.

The supporting role of the fibroblast, which is the major cell present in the stroma surrounding a tumour, has been highlighted in a number of diverse investigations. Ductal carcinoma of the breast has frequently been associated with fibrosis[1] and human breast cancer cells lines *in vitro* release chemoattractants for fibroblasts[2]. Colonic cancer cells secrete factors that enhance the ability of colonic fibroblasts to remodel the collagen matrix *in vitro*[3]. Furthermore, fibroblasts have long been used as feeder or supporting cells for cultures of various tumours *in vitro*[4,5].

The capacity of the fibroblast to facilitate tumour cell growth might be mediated in two ways: by cell-to-cell contact or by factors secreted by fibroblasts such as extracellular matrix constituents (e.g. collagen) or growth factors (e.g. fibroblast growth factor (FGF)). Support for the former comes from a study in which co-inoculation of primary breast skin fibroblasts with breast cancer cell lines *in vivo* resulted in an increase in tumour take and growth compared with that in controls. When the fibroblasts added to the cancer cell inoculum were killed by glutaraldehyde, tumour take was increased but growth was not; when the fibroblasts were lethally irradiated, tumour growth was enhanced but not to the same degree as when live fibroblasts were used[6,7]. The same groups identified a fibroblast-derived factor mitogenic to breast cancer cells, which was isolated and partially characterized[8]. Using a similar model, Noel and co-workers[9] demonstrated that the addition of fibroblasts and fibroblast-conditioned media to human breast adenocarcinoma cell inocula enhanced tumorigenicity. The helper effect of fibroblasts for different tumour types has been demonstrated[6,7,9–11]. One study[12] has demonstrated fibroblast facilitation of LS174T colorectal cancer cell take, by inoculation with murine fibroblasts. To the authors' knowledge, no other work has been conducted with colorectal cancer cells.

The authors have previously described a regenerating rat liver model which supports metastases[13]. In this model 'metastases' were established by intraportal inoculation of syngeneic tumour cells at different time intervals after two-thirds partial hepatectomy. After partial hepatectomy the implantation of tumour cells resulted in a dramatic increase in tumour take, especially when cells were injected between 2·5 and 5 days after surgery. This event could have been due to the Ito cells, since the time window of 'fertility' includes the period of proliferation within the liver of non-hepatocytes (Ito cells (specialized fibroblasts), Kupffer cells (resident macrophages) and endothelial cells which line the sinusoids).

In this study the effect of fibroblasts isolated from regenerating rat liver at different time intervals after partial hepatectomy on the growth of human colorectal cancer cells was investigated in an *in vivo* model.

Materials and methods

Extraction and growth of primary fibroblasts

Syngeneic adult hooded Lister rats of either sex (280–350 g) were obtained from the Chester Beatty Institute (London, UK) and maintained as an inbred line. Two-thirds partial hepatectomy was performed according to the method of Higgins and Anderson[14]; this consisted of the ligation and excision of the median and left lobes of the rat liver with the right and caudate lobes remaining intact.

Livers were harvested from four groups of animals killed at the following times: (1) 2·5 days after partial hepatectomy and (2) 4 days after partial hepatectomy (at these times previous experiments had shown the liver to be highly susceptible to growing liver metastases); (3) day 1 after partial hepatectomy; and (4) normal liver. In the latter two groups liver parenchyma had been shown[13] to be relatively refractive to tumour take.

Liver tissue (2–3-mm³ fragments) was enzymatically disaggregated with protease 0·5 mg/ml and DNAse 0·005 mg/ml (Sigma, Poole, UK) at room temperature for 20 min using a slow magnetic stirrer. The enzymatic disaggregation was too harsh for

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the preservation of hepatocytes, which were thus excluded from the cultures. The pulp was sedimented at 1*g* and the supernatant containing monodispersed cells was washed by centrifugation at 350*g* for 5 min. The cells were resuspended in McCoy's 5A medium (GIBCO BRL Life Technologies, Paisley, UK) containing 20 per cent fetal calf serum (FCS) (Imperial Laboratories, Andover, UK), penicillin–streptomycin 100 μg/ml (GIBCO BRL Life Technologies) and glutamine 100 μg/ml (GIBCO BRL Life Technologies), plated in 25-cm^2 flasks under sterile conditions and incubated in a humidified atmosphere of 5 per cent carbon dioxide at 37°C. Cells were either assayed for *in vitro* growth or, when confluent, enzymatically disaggregated (trypsin 0·05 mg/ml ethylenediamine tetra-acetic acid 0·005 mg/ml (GIBCO BRL Life Technologies)) and used for the *in vivo* experiments.

In vitro *growth studies*

Primary fibroblasts were characterized by means of: (1) morphological characteristics, with fixed cultures stained with methylene blue and eosin (Romanowski stain, DiffQuik) (HARLECO, Liege, Belgium) for visualization; and (2) two histochemical markers, vimentin for mesenchymal cells (using a monoclonal primary anti-vimentin antibody (M725; DAKO, High Wycombe, UK) and a standard ABC kit (DAKO)) and non-specific esterase for monocytes, to detect Kupffer cells, using a naphthol butyrate substrate and counterstained with methyl green[15] (Sigma). The markers were applied on the liver cells immediately after disaggregation and also on the cell populations once they had been grown in culture for several days.

Parallel cultures of primary fibroblasts (from at least five livers at each time point after partial hepatectomy) were cultured in McCoy's medium (described above) for 3, 4, 6 and 8 days. Cells were fixed and stained with methylene blue (Merck, Poole, UK), which binds to nucleic acids stoichiometrically[16].

In vivo *growth studies*

Experiments were carried out using 84 Balb/c mice obtained from Harlan-Olac (Bicester, UK) and maintained in isolation. Tumour cells with and without fibroblasts were inoculated subcutaneously, under ether anaesthesia. The experimental groups consisted of animals receiving primary fibroblasts together with HT29 colorectal cancer cells (European Collection of Cell Cultures, Porton Down, UK) in a ratio of 1:10 ($10^5:10^6$). Control groups consisted of animals receiving tumour cells, those receiving fibroblasts alone (fibroblast line cells C3H10T 1/2 (European Collection of Cell Cultures) and primary cells from groups 1 and 2), and those receiving tumour cells and fibroblast line cells C3H10T 1/2 in a ratio of 1:1 ($10^6:10^6$).

The animals were killed and autopsy was performed after 3 weeks. Tumours were excised and weighed. Routine histological examination (haematoxylin and eosin stain; Merck) was performed on paraffin-embedded material. Also, fresh tumour biopsies were taken into normal saline, disaggregated with protease and DNAse (as described above) and the resultant cell suspension was returned to culture, to observe the nature of the viable cell populations.

Results

Growth of primary fibroblasts in vitro

Rat livers were disaggregated to provide primary fibroblast cultures. Romanowski stain on fixed cultures revealed large numbers of lightly stained bipolar cells which on confluence became organized into parallel arrays and whorls with orthogonal overlapping. There was a small number of round darkly stained cells that were present in all cultures but seemed to persist rather than grow.

Histochemical staining was performed on liver cells immediately after disaggregation and on cells that had grown in culture for at least 1 week. Vimentin positivity was between 2 and 8 per cent for disaggregated cells, but after the cells were allowed to grow in culture for 1 week vimentin positivity was greater than 95 per cent. This suggested that the vimentin-positive cells (fibroblasts) proliferated *in vitro*. In contrast non-specific esterase staining started at 15–44 (median 30) per cent in the disaggregated cells and fell to between 2 and 30 (median 15) per cent for cells that had grown in culture. This suggests that Kupffer cells merely persist in culture.

To determine the possible effect of Kupffer cells on the growth of fibroblasts *in vitro*, the two populations (fibroblasts and Kupffer cells) were separated by plating in serum-free medium for 30 min and then removing and plating the supernatant containing non-adherent cells (fibroblasts). The adherent cultures, containing mainly Kupffer cells, exhibited little growth. Some cells eventually grew in these flasks but were identified as fibroblasts remaining after the separation. The non-adherent cultures, containing primarily fibroblasts, grew as well as the controls that contained both cell populations (data not supplied).

The growth rate of primary fibroblasts *in vitro* depended on the state of regeneration of the livers. There were two types of cultures: those that exhibited 'fast' proliferation and those that were relatively 'slow' (*Fig. 1*). Experiments

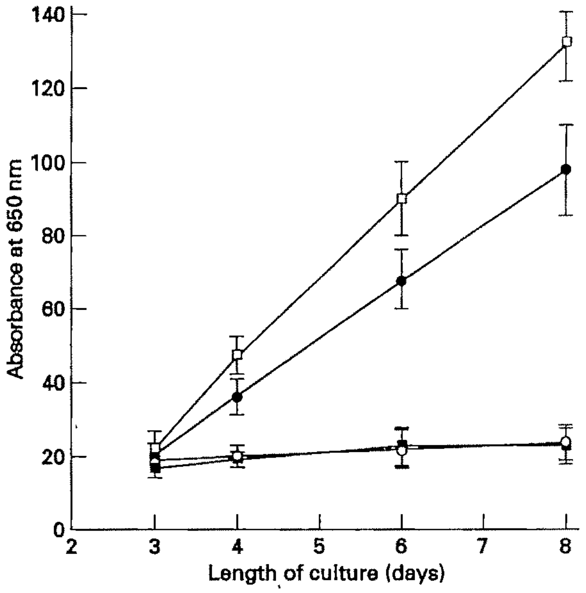

Fig. 1 *In vitro* growth of primary fibroblasts. Normal and partially hepatectomized livers (at 1, 2·5 and 4 days after partial hepatectomy) were disaggregated enzymatically. The resultant cells were cultured for 3, 4, 6 and 8 days, fixed and stained with methylene blue. Dye eluted from cells (equivalent to biomass) was quantitated spectrophotometrically at 650 nm. Mean(s.e.m.) values for five livers were plotted. Each point (per liver preparation) was read in sextuplicate. Growth curves for fibroblasts from normal liver (■) and liver on day 1 after partial hepatectomy (○) were virtually superimposed. After 6 days of culture, growth of both normal and day 1 fibroblasts was significantly different from that of fibroblasts harvested at 2·5 days (●) and 4 days (□) after partial hepatectomy ($P<0{\cdot}02$, Student's *t* test)

were conducted to determine the exact times after partial hepatectomy when cultures were either fast or slow. Slow cultures always grew from normal livers, from livers taken early after partial hepatectomy (e.g. 1 day) and from those taken late after partial hepatectomy (e.g. 12 days). Fast growth of cells was first observed in some cultures from day 2 after hepatectomy: cell growth was rapid, yielding high numbers of colonies, if the livers were left to regenerate for just over 48 h; however, cultures were slow to grow and were quite similar to those from normal livers if the livers were removed before 48 h of regeneration were completed. 'Fast' cultures always resulted from cells derived from livers at 3, 4 and 5 days after partial hepatectomy. Proliferation started slowing down by day 6 and eventually reached background levels. This suggests that 'activation' of the fibroblasts is in some way related to the stage of regeneration of the liver.

Results are shown for fibroblasts harvested on days 1, 2·5 and 4 after partial hepatectomy and from normal liver (*Fig. 1*) since these were the time points used for the *in vivo* experiments. The growth curves for fibroblasts from normal liver and those harvested on day 1 were similar. There was no significant difference between the growth rates of fibroblasts harvested on days 2·5 and 4, but there was a significant difference between the 'slow' curves (day 1 after partial hepatectomy and normal liver) and both of the 'fast' curves ($P < 0{\cdot}02$, Student's *t* test).

Growth of tumour cells in vivo

Nude mice were inoculated subcutaneously with tumour cells with and without fibroblasts. The presence of tumour was confirmed histologically in all groups.

The results for tumour growth for all groups of animals are shown in *Fig. 2*. Forty-three per cent of animals receiving tumour cells alone developed a subcutaneous tumour after 3 weeks. The group of mice that received both tumour cells and cell line fibroblasts (C3H10T 1/2) ($n = 18$) showed a higher incidence of tumour take (75 per cent) than the tumour-only group. However, tumour size was similar in the two groups (median weight 0·3 g in the tumour group *versus* 0·4 g in the tumour–fibroblast group).

When 'slow' primary liver fibroblasts were added to tumour cells (1:10; $n = 12$), tumour was present in 75 per cent of animals and tumour size was no different from that in control animals. The addition of 'fast' liver fibroblasts to tumour cells (1:10; $n = 15$) increased the tumour take to 100 per cent and also significantly increased tumour weight: the minimum weight recorded was 0·5 (median 3·5) g.

Control animals inoculated with either fast fibroblasts or C3H10T 1/2 cells exhibited no growth after 3 weeks (results not shown). The slow fibroblasts were not inoculated by themselves as a control.

Tumour samples were taken at autopsy, enzymatically disaggregated and cultured to assess the nature of cells that had grown *in vivo*. Disaggregates of the tumour-alone group grew primarily as epithelial cells. A small number of fibroblast-like cells was present in the initial culture, remaining relatively quiescent for the first 7 days, while the cancer cells formed colonies. Eventually the fibroblasts also started growing as a patchy monolayer, surrounding the tumour colonies but never overtaking them. Samples from animals that had received both tumour cells and fibroblasts were also disaggregated and cultured, with similar results.

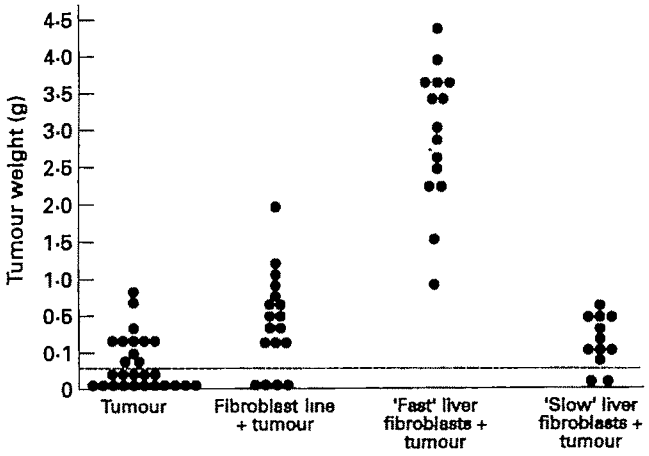

Fig. 2 Effect of fibroblasts on the growth of tumour cells *in vivo*. The human colorectal cell line HT29 (10^6 cells) was inoculated in nude mice alone or with different types of fibroblasts: the fibroblast cell line C3H10T 1/2 (tumour cells : fibroblasts ratio 1:1), 'fast' primary fibroblasts harvested from livers 2·5 and 4 days after partial hepatectomy (tumour cells : fibroblasts ratio 10:1), 'slow' primary fibroblasts from normal liver and livers 1 day after partial hepatectomy (tumour cells : fibroblasts ratio 10:1). At 3 weeks, tumour take (presence of tumour) and tumour growth (weight of tumour) were assessed. Failure to grow is depicted under the dotted line. Each dot represents a tumour. Tumour take and tumour growth were significantly higher for the tumour plus 'fast' fibroblasts compared with all other groups (tumour take 100 *versus* 42–75 per cent; $P < 0{\cdot}03$, Mann–Whitney *U* test; median tumour size 3·5 *versus* 0·3–0·4 g; $P < 0{\cdot}02$, Mann–Whitney *U* test)

Discussion

The proliferating cell population derived from the rat liver in these experiments consisted of fibroblasts, as demonstrated by morphology and immunohistochemistry. The cells exhibited two distinct *in vitro* growth patterns: fibroblasts from normal liver and those harvested 1 day after partial hepatectomy were much slower to grow than those extracted from livers 2·5 and 4 days after surgery.

Fibroblasts can exhibit different phenotypic or functional characteristics, depending on their environment; fibroblasts from regenerating liver, healing wounds, tissues with fibroactive disease (myofibroblasts) and tumour stroma (desmoplastic fibroblasts) are believed to share functional and structural characteristics, such as the expression of α-smooth actin[2,3,17–20]. The difference in growth patterns reported in this study could be associated with the state of regeneration of the liver at the time of excision.

The major activity in the liver 24 h after partial hepatectomy is hepatocyte proliferation, whereas the cells isolated were 'slow' fibroblasts. There is no evidence of non-hepatocyte proliferation – of Kupffer cells (resident macrophages), Ito cells (specialized fibroblasts) or endothelial cells (which line the sinusoids) – at this time. The presence of proliferating non-hepatocytes in normal healthy liver is also rare[21–23].

The 'fast' fibroblasts were derived from liver at times when non-hepatocytes have been shown to proliferate within the regenerating liver[13,22,23]. The signal for fibroblast proliferation in the liver may be growth factors released from other cell populations, such as hepatocytes or extrahepatically recruited monocytes[22–24]. The presence or absence or Kupffer cells did not affect fibroblast growth *in vitro*, suggesting that Kupffer cells were not providing any mitogenic factors necessary for the fibroblasts. This, of course, does not preclude that *in vivo* there may be a mechanism by which Kupffer cell products 'turn on' fibroblasts (or rather, Ito cells)[25]. However, *in vitro* models suggest that liver fibroblasts are capable of establishing their own paracrine or autocrine stimulation loops, and demonstrate FGF-like growth factors[26,27].

In vivo co-inoculation of HT29 tumour cells with fibroblasts resulted in an increase in tumour growth and take, which was dependent on the 'type' of fibroblast used in each group. The addition of either cell line fibroblasts or 'slow' primary fibroblasts increased tumour take but not growth. Using the same tumour cell line, Hennigan and co-workers[12] found that the addition of human skin fibroblasts increased both take and growth of tumour. The difference may be partly attributable to species differences or to the higher tumour inoculum in their study; the latter may also explain the higher take (52 per cent) these workers reported in the tumour-alone group. Tumour take and growth were the same in the present two groups, even though the number of cells inoculated with the fibroblast cell line was ten times greater than that for the 'slow' fibroblasts. This may either be a reflection of the difference between primary cells and established lines or may be due to the presence of small numbers of Kupffer cells in the inocula.

The enhancing effect of fibroblasts on tumour growth has been demonstrated in a number of *in vivo* tumour models[6,7,9–12]. In particular, work in breast cancer models[6,7,9] has shown that, when co-inoculated with tumour, live fibroblasts are more stimulatory than killed fibroblasts. The effect on tumour growth was even greater with the addition of matrigel (a cocktail of basement membrane proteins) or fibroblast-conditioned media to the inocula[9], suggesting that factors secreted by the cells are important rather than the mere presence of fibroblasts. Additionally, fibroblasts or fibroblast-conditioned media enhances breast cancer cell growth *in vitro*[8,28]. The putative growth factors have not been positively identified, although an 8-kDa protein was isolated in a breast model[8], providing further evidence that the effect by fibroblasts is humorally mediated. Fibroblasts may also enhance tumour growth by the production of extracellular matrix components, e.g. collagens I and III and fibronectin, creating a favourable environment for tumour cell survival[17–20].

In the present study, the addition of 'fast' primary fibroblasts had a profound effect on both take and growth of tumour *in vivo*. These cells may have properties akin to those of myofibroblasts and desmoplastic fibroblasts, as discussed previously. A number of workers have studied fibroblasts which, although not specifically defined by this terminology, were present in tumour stroma or healing tissues or which exhibited behaviour associated with myofibroblasts or desmoplastic fibroblasts. These studies suggest two mechanisms by which this type of fibroblast may enhance tumour growth.

First, in co-cultures of breast cancer cells and fibroblasts derived from tumour stroma, both cell populations are stimulated to proliferate. The fibroblasts secrete growth factors that are unlike either epidermal growth factor or insulin[28]. In an *in vitro* model of healing, conditioned media from fibroblasts derived from healing tissue were shown to secrete approximately four times as much platelet-derived growth factor (PDGF) than fibroblasts derived from normal tissue[29]. It is possible that a growth factor such as PDGF secreted by the tumour stroma may stimulate growth of either stromal or tumour cells, in an autocrine–paracrine fashion[30].

Second, fibroblasts can manipulate both the production and dissolution of extracellular matrix. Myofibroblasts have been shown to overproduce matrix components, such as collagen IV[17–20]. This would contribute positively to the environment provided for tumour cell growth. Furthermore, fibroblasts present in the tumour stroma have been shown immunohistochemically to secrete matrix-degrading enzymes such as gelatinase (collagenase IV) and stromelysin in both colorectal and breast cancer but not in the normal colon or breast[20,31–33]. Such enzymes would ultimately be necessary for dissolution of the extracellular matrix and subsequent tumour invasion.

Experiments that assessed the proliferative rate of xenografted tumours (HT29) 20 days after inoculation[12] suggested that the initial survival but not the subsequent growth of colorectal cancer cells was promoted by inoculation with fibroblasts.

The phenomenon observed (the enhancement of tumour growth when in contact with fibroblasts) correlates with the microinjury hypothesis of metastasis. This hypothesis states that the arrest of blood-borne cancer cells at a vascular site (for example, non-deformable carcinoma cells in a capillary bed) causes 'microinjury' and subsequent healing at the site, which enhances the metastatic process[34,35]. Part of the healing process is the recruitment of fibroblasts, which act as secretors of growth factors and orchestrators of refashioning of the extracellular matrix. The 'fast' fibroblasts used in the present study are derived from the regenerating liver and may act in a similar way to fibroblasts from a healing process; as a consequence they may also be supportive of tumour cell growth.

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Prospective study of hand-sutured anastomosis after colorectal resection

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A total of 370 patients underwent colorectal resection: 320 had a primary single-layer seromucosal anastomosis without a protective colostomy, 22 had Hartmann's procedure and 28 abdominoperineal resection. There were 260 elective procedures and 110 patients had peritonitis and/or bowel obstruction at the time of surgery. Overall the mortality rate was 2·7 per cent, the morbidity rate was 18·3 per cent and clinical anastomotic leak rate 3·4 per cent. After elective operation, the leak rate for intraperitoneal anastomosis was 0·6 per cent and for low extraperitoneal anastomosis 7 per cent. The mortality rate was 1·2 per cent and morbidity rate 11·9 per cent. Patients with peritonitis had a significant increase in morbidity rate (46 per cent) in comparison with those having elective surgery ($\chi^2 = 31{\cdot}5$, 1 d.f., $P < 0{\cdot}0001$). Patients who had bowel obstruction and no bowel preparation had a significantly higher morbidity rate of 26 per cent and mortality rate of 7 per cent, compared with those having an elective procedure ($\chi^2 = 11{\cdot}2$, 1 d.f., $P < 0{\cdot}001$; $\chi^2 = 8{\cdot}7$, 1 d.f., $P < 0{\cdot}005$ respectively). Patients having palliative surgery had the highest mortality rate (19 per cent), compared with those operated on with curative intent (1·5 per cent) ($\chi^2 = 28{\cdot}7$, 1 d.f., $P < 0{\cdot}0001$). Cost-saving hand-sutured anastomosis is effective and, in experienced hands, technically feasible after all kinds of colorectal resection and should remain the standard in colorectal surgery.

Many different techniques are used for intestinal anastomosis following resection. For low colorectal anastomosis, in particular, there is still a high risk of leakage. There have been claims of a reduced leak rate following the introduction of the anastomotic stapling gun[1], fewer protective colostomies and lower anastomoses[2,3]. In 1985 Hardy *et al.*[4] described a biofragmentable anastomosis ring (BAR), which facilitated sutureless atraumatic anastomosis. The history of bowel anastomosis is replete with studies comparing different methods, such as absorbable *versus* non-absorbable sutures[5–7], inverting *versus* everting techniques[8,9], one- *versus* two-layer procedures[10–12], sutures *versus* staples[3,8,13–15], and sutures *versus* BAR[16,17]. No single method of anastomosis has proved superior. All surgeons agree on the requisite qualities for the ideal anastomosis: an adequate blood supply, accurate serosal apposition with no tension at the suture line and an uncompromised lumen with a water-tight seal. Many still prefer a hand-sutured anastomosis, which remains the ultimate standard for all colorectal anastomoses.

In this study all patients who had colorectal resection were recorded prospectively to evaluate the safety and efficacy of hand-sutured anastomosis in unselected patients in a district hospital.

Patients and methods

Between January 1991 and December 1993, 370 consecutive patients had colorectal resection, 320 of whom had a primary anastomosis. The median age was 67 (range 20–94) years.

In elective cases without obstruction the bowel was prepared by orthograde whole-gut irrigation via a nasogastric tube using Ringer lactate solution. In emergency operations or large bowel obstruction, irrigation was performed during operation via the appendix Standard single-dose parenteral antibiotic prophylaxis was used and all patients received perioperative heparin.

The abdomen was opened through a midline incision. In left colonic or rectal resections, the entire left colon and splenic flexure were mobilized routinely. The bowel was freed from the mesocolon and appendices epiploicae over less than 1 cm for anastomosis, and the arcade vessels were transected without clamps to evaluate blood supply. Total mesorectal excision was performed for rectal cancer. Anastomoses were carried out using 12–16 interrupted seromucosal 4/0 polyglactin sutures in an inverting single-layer technique.

Protective colostomies were not used. In patients with diffuse peritonitis due to bowel perforation, Hartmann's procedure was performed with an end-sigmoid colostomy. In patients with localized peritonitis due to diverticulitis, after resection, primary anastomosis was the standard procedure

Routine contrast enema was not performed after operation. Anastomotic leak was suspected if the patient showed fever, leucocytosis, persistent ileus, bleeding or discharge, or any other sign of intra-abdominal or pelvic abscess In these cases a water-soluble contrast enema was carried out immediately.

For statistical analysis comparison of continuous variables was by means of Student's t test, using the χ^2 test for qualitative variables. Correlation of two variables was evaluated with the correlation coefficient r. $P \leq 0{\cdot}05$ by a two-tailed test was considered statistically significant

Results

Of 370 patients who had colonic or rectal resection, 320 had a primary anastomosis and 50 a temporary (22) or permanent (28) colostomy in 260 elective procedures and 110 emergency operations. Surgical diagnosis, operative procedures and complications are shown in *Tables 1–3*. The morbidity rate was significantly higher in patients with peritonitis (46 per cent) than in elective patients (11·9 per cent) ($\chi^2 = 31{\cdot}5$, 1 d.f., $P < 0{\cdot}0001$). There were 28 primary intraperitoneal anastomoses in cases of localized peritonitis, after sealed diverticular perforation, and 15 Hartmann's procedures, when peritonitis affected the whole peritoneal cavity. In the former cases the leak rate (two of 28 (7 per cent)) was significantly higher than for elective intraperitoneal anastomosis (one of 170 (0·6 per cent)) ($\chi^2 = 6{\cdot}9$, 1 d.f., $P < 0{\cdot}01$). In 78·6 per cent of patients with bowel obstruction, primary anastomosis was

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Table 1 Clinical details

Localization	Carcinoma	Diverticulitis	Crohn's disease or colitis	Adenoma	Other*	Total
Caecum	16	0	6	3	5	30
Ascending colon	27	0	2	4	1	34
Right flexure	10	0	0	0	1	11
Transverse colon	9	0	0	5	1	15
Left flexure	13	0	1	0	1	15
Descending colon	8	3	1	0	1	13
Sigmoid	62	52	0	11	3	128
Entire colon	5	0	1	1	3	10
Rectum	94	0	2	13	5	114
Total	244	55	13	37	21	370

*Four patients had ischaemic necrosis, three traumatic perforation, six lower intestinal bleeding, five abscess and four rectovaginal fistula

Table 2 Operative morbidity and mortality

Type of resection	No. of patients	Morbidity	Leak	Mortality
Caecal resection	14	3 (21)	0 (0)	0 (0)
Right hemicolectomy	54	6 (11)	0 (0)	3 (6)
Left hemicolectomy	19	5 (26)	1 (5)	1 (5)
Transverse colectomy	8	1 (12)	0 (0)	0 (0)
Sigmoid colectomy	89	15 (17)	3 (3)	1 (1)
Segment resection	15	2 (13)	0 (0)	0 (0)
Subtotal colectomy	16	4 (25)	1 (6)	1 (6)
Local excision	10	1 (9)	0 (0)	0 (0)
Reanastomosis after Hartmann's operation	22	5 (23)	0 (0)	1 (5)
Laterolateral colostomy	3	0 (0)	0 (0)	0 (0)
Low colorectal anastomosis	55	9 (16)	5 (9)	0 (0)
Coloanal anastomosis	7	1 (14)	0 (0)	0 (0)
Parasacral trans-sphincteric resection (Mason)	8	2 (25)	1 (12)	0 (0)
All anastomoses	320	54 (16·9)	11 (3·4)	7 (2·2)
Hartmann's operation	22	8 (36)	0 (0)	2 (9)
Abdominoperineal resection	28	6 (21)	0 (0)	1 (4)

Values in parentheses are percentages

Table 3 Postoperative complications in 370 patients*

Complication	Colon ($n=256$)	Rectum ($n=114$)	Total ($n=370$)
Subcutaneous wound infection	16 (6·2)	10 (8·8)	26 (7·0)
Subfascial wound infection	1 (0·4)	0 (0)	1 (0·3)
Anastomotic leak	5 (2·1)	6 (7·0)	11 (3·4)
Stomal necrosis	1 (5)	1 (4)	2 (4)
Bleeding	2 (0·8)	2 (1·8)	4 (1·1)
Persistent peritonitis	3 (1·2)	1 (0·9)	4 (1·1)
Subphrenic abscess	1 (0·4)	0 (0)	1 (0·3)
Intra-abdominal abscess	3 (1·2)	0 (0)	3 (0·8)
Postoperative ileus	4 (1·6)	2 (1·8)	6 (1·6)
Complete wound dehiscence	5 (2·0)	0 (0)	5 (1·4)
Systemic complication	17 (6·6)	6 (5·3)	23 (6·2)

Values in parentheses are percentages. *Includes 320 anastomoses and 50 colostomies

performed after intraoperative lavage. In these patients morbidity and mortality rates were significantly higher than those in elective, prepared patients (morbidity rate 26 *versus* 11·9 per cent respectively, $\chi^2=11{\cdot}2$, 1 d.f., $P<0{\cdot}001$; mortality rate 7 *versus* 1·2 per cent respectively, $\chi^2=8{\cdot}7$, 1 d.f., $P<0{\cdot}005$). The mortality rate after palliative resection was also significantly higher at 19 per cent (five of 26 patients) compared with surgery for curative intent at 1·5 per cent (five of 344) ($\chi^2=28{\cdot}7$, 1 d.f., $P<0{\cdot}0001$).

There were 81 extraperitoneal low colorectal anastomoses in 51 women and 30 men. There was no significant difference between leak rate in women (five of 51) and men (one of 30).

Nine of 11 patients with a leak required reoperation; two with failure of an extraperitoneal low rectal anastomosis were successfully managed conservatively. A further 17 patients also needed a second surgical procedure: four with persistent peritonitis after sigmoid perforation, two with intra-abdominal abscess, four with bleeding, four with deep and two with superficial wound infection, and one with subphrenic abscess. Three of the 11 patients with an anastomotic leak died and there were seven other postoperative deaths due to systemic complications (*Table 2*).

Discussion

Various types of automatic stapling device are popular in colorectal surgery[18,19] and some surgeons have favoured the BAR in recent years[20,21]. Prospective studies have, however, failed to prove these procedures superior to a hand-sutured anastomosis[15–17]. There are problems with the technical feasibility of stapled anastomosis, particularly in low extraperitoneal rectal anastomosis, and there may be more clinical or radiological leakage[14,22]. It has been claimed that use of the staple gun has reduced the rate of abdominoperineal resection, especially in men with a narrow pelvis, and also the number of protective colostomies[3,19], but there has been no properly controlled trial to substantiate this.

The results of the present series are comparable with those of other prospective studies[15,22,23], documenting an overall clinical leak rate of 3·4 per cent. The radiological leak rate is at least twice the clinical leak rate[15,22,24] and is subject to individual interpretation. In this study routine postoperative contrast enemas were not given unless there was clinical suspicion of anastomotic failure.

It was the authors' policy not to employ a protective colostomy when carrying out a primary anastomosis;

whenever this seemed too dangerous, Hartmann's procedure was preferred, a strategy supported by the present data. In 43 patients with peritonitis, 28 primary anastomoses and 15 Hartmann operations were carried out, and in 103 patients with bowel obstruction 81 primary anastomoses and 22 Hartmann procedures were performed. The morbidity rate was significantly higher than in patients undergoing elective surgery in both groups, and the mortality rate was higher in those with bowel obstruction. Mortality rate was not higher in patients with peritonitis despite the fact that primary anastomosis was done in 65 per cent of cases. The leak rate was higher in patients with peritonitis and intraperitoneal anastomosis than in those having an elective procedure (7 *versus* 0·6 per cent; $\chi^2 = 6{\cdot}9$, 1 d.f., $P < 0{\cdot}01$), although not in patients with bowel obstruction who had a primary anastomosis.

A surgeon who can insert a purse-string suture into the rectal stump via the abdomen should be able to perform a sutured anastomosis in both men and women[15]. Anastomosis at the anal verge can easily be performed from below. All abdominoperineal resections in this series were performed for oncological considerations, i.e. carcinoma larger than T_2, when an intersphincteric resection with coloanal anastomosis would not have been sufficiently radical. The time taken for anastomosis is reduced only marginally by stapling and no significant difference in operating time has been documented between stapled or sutured anastomoses[13,15,25]. The comparison of cost between the different techniques is obvious: the suture material for a hand-sutured anastomosis costs less than £25, whereas the various stapling devices or the BAR cost between £100 and £250 for the device alone[15,22,26].

Neither stapled anastomosis nor the sutureless BAR has proved superior to conventional hand-sutured anastomosis[15,16,17,22]. The data from this prospective series are comparable with results reported by others[15,16,22,27] and confirm that hand-sutured anastomosis is equally effective, cost saving and, in experienced hands, technically feasible after all kinds of colorectal resection. The interrupted single-layer hand-sutured anastomosis remains the ultimate standard in colorectal surgery.

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Total pelvic exenteration for locally advanced colorectal carcinoma

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Twenty-six patients who underwent total pelvic exenteration for locally advanced colorectal cancer were studied retrospectively. The operative mortality rate was 8 per cent (two deaths). In patients with stage II primary disease the recurrence rate after curative surgery was three of seven, although the mean survival time was 58 months and the 5-year survival rate 71 per cent. Patients with stage III primary disease had a shorter mean survival time regardless of supposed curability (curative 14 months *versus* non-curative 9 months). Patients with stage IV disease had a mean survival time of 5 months. In patients who underwent curative surgery for recurrent disease the mean survival time was 33 months and 5-year survival rate 25 per cent, although in those receiving non-curative surgery the survival time was significantly shorter at 10 months ($P < 0.05$). Total pelvic exenteration is warranted for patients with stage II locally advanced colorectal carcinoma and is an option for those with recurrent carcinoma when performed with curvative intent.

Total pelvic exenteration for advanced colorectal carcinoma localized to the pelvic region remains a formidable, albeit potentially curative, procedure. Complete removal of involved adjacent organs such as the vagina, uterus, bladder and prostate gland can be effective in controlling local disease and improving palliation. However, complications are more severe than following standard resection for colorectal carcinoma[1–6]. The 5-year survival rate after radical pelvic exenteration varies from 32 to 79 per cent[1–5] and the prognosis in selected patients can be excellent. This study was designed to review total pelvic exenteration performed for locally advanced colorectal carcinoma.

Patients and methods

Total pelvic exenteration was performed on 26 patients with primary or recurrent colorectal carcinoma between January 1975 and March 1992. These patients were studied retrospectively. Seventeen patients (14 men, three women) had primary carcinoma and were of mean age 55 (range 42–88) years; nine patients (three men, six women) had recurrent carcinoma and mean age of 57 (range 47–69) years.

Preoperative evaluation of the depth of tumour invasion and the presence of liver, lung and lymph node metastases was performed by digital examination., barium enema, colonoscopy, endoluminal ultrasonography, chest radiography, intravenous urography, cystoscopy, computed tomography (CT) and magnetic resonance imaging (MRI). In addition the diagnosis was confirmed histologically by biopsy, either before or during operation whenever possible.

Preoperative radiotherapy was given to three patients, two with primary and one with recurrent disease. After operation, all patients received either 5-fluorouracil or 1-hexylcarbamoyl-5-fluorouracil orally, but radiotherapy was not used.

Surgical specimens were prepared as reported previously and stained with haematoxylin and eosin, and elastica van Gieson[7] stain. They were reviewed by one author (K.S.), who made the histopathological diagnosis including histological type, depth of tumour invasion and presence of lymph node metastasis. The pathological stage was defined according to the fourth edition of the Union Internacional Contra la Cancrum tumour node metastasis classification[8,9]. Stage II disease is defined as a tumour of stage T_3 (invading through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues) or T_4 (perforating the visceral peritoneum or directly invading other organs or structures), N_0 (no regional lymph node metastasis) and M_0 (no distant metastasis). Stage III disease is defined as a tumour of any T stage, N_{1-3} (lymph node metastasis) and M_0. Stage IV disease is defined as a tumour of any T stage with M_1 (distant metastasis).

The follow-up investigation was carried out by outpatient visits, letter or telephone. The final follow-up date of the study was 30 November 1994. Patients had a postoperative protocol surveillance including tumour marker measurement, chest radiography and ultrasonography every month for the first year, then 3-monthly. CT or MRI was performed 6-monthly for the first year, then annually. Recurrent tumour was determined by the measurement of serum carcinoembryonic antigen level and by findings on chest radiography, ultrasonography, CT and MRI. The site of first recurrence was recorded for each patient and defined as within the pelvis, distant recurrence or intraperitoneal dissemination.

All data were entered into a personal computer with dBASE III Plus software (Ashton–Tate, Torrance, California, USA). The Kaplan–Meier method[10] was used to calculate survival rates; significant differences in rates were assessed with the log rank test[11]. Significance was defined at $P < 0.05$.

Results

Clinical findings in the 17 patients with advanced primary colorectal cancer are detailed in *Table 1*. Most patients received an ileal conduit as described by Bricker[12]. Findings in the nine patients with recurrent colorectal carcinoma are shown in *Table 2*, together with details of the original surgery. The adjacent organs invaded by these locally advanced tumours are reported in *Table 3*. In four patients with primary tumours there was no histological evidence of invasion despite the surgical findings.

The overall perioperative morbidity and mortality rates were 31 per cent (eight patients) and 8 per cent (two) respectively. Four of the 17 patients with primary tumours had major postoperative complications. One developed an ileoperineal fistula secondary to ileoileal anastomotic dehiscence; this patient had received radiotherapy for cervical cancer 19 years previously. Several reoperations were necessary but she recovered and has survived 3 years to date. Two patients had postoperative ileus that recovered with conservative therapy. The remaining patient, who received preoperative radiotherapy for primary disease, died from pelvic sepsis 20 days after operation.

Four of the nine patients who underwent exenteration for recurrent carcinoma had major postoperative

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Table 1 Clinical findings in patients with primary colorectal cancer

Patient no.	Age (years)	Sex	Site of tumour	Histological type	Stage	Urinary diversion
1	47	M	Rectosigmoid	Well differentiated adenocarcinoma	II	Ureterocutaneostomy
2	48	M	Lower rectum	Well differentiated adenocarcinoma	II	Ileal conduit
3	59	M	Upper rectum	Well differentiated adenocarcinoma	II	Ileal conduit
4	50	M	Lower rectum	Well differentiated adenocarcinoma	II	Ileal conduit
5	74	M	Lower rectum	Well differentiated adenocarcinoma	II	Ureterocutaneostomy
6	48	M	Upper rectum	Well differentiated adenocarcinoma	II	Ureterocutaneostomy
7	58	F	Lower rectum	Mucinous adenocarcinoma	II	Ileal conduit
8	49	F	Upper rectum	Well differentiated adenocarcinoma	III	Ileal conduit
9	42	M	Lower rectum	Moderately differentiated adenocarcinoma	III	Ileal conduit
10	51	M	Upper rectum	Well differentiated adenocarcinoma	III	Ileal conduit
11	52	M	Lower rectum	Moderately differentiated adenocarcinoma	III	Ileal conduit
12	57	F	Lower rectum	Well differentiated adenocarcinoma	III	Ileal conduit
13	54	M	Lower rectum	Moderately differentiated adenocarcinoma	III	Ileal conduit
14	61	M	Lower rectum	Well differentiated adenocarcinoma	III	Ileal conduit
15	53	M	Lower rectum	Poorly differentiated adenocarcinoma	III	Ileal conduit
16	88	M	Lower rectum	Moderately differentiated adenocarcinoma	IV	Ileal conduit
17	45	M	Upper rectum	Moderately differentiated adenocarcinoma	IV	Ureterocutaneostomy

Table 2 Clinical findings in patients with recurrent colorectal cancer

Patient no.	Age (years)	Sex	Site of primary	Histological type	Original stage	Original operation	Urinary diversion
18	63	F	Anal canal	Signet ring cell carcinoma	I	APR	Ileal conduit
19	69	M	Rectosigmoid	Well differentiated adenocarcinoma	II	Anterior resection	Ureterocutaneostomy
20	67	F	Lower rectum	Mucinous adenocarcinoma	II	APR	Ileal conduit
21	64	M	Rectosigmoid	Moderately differentiated adenocarcinoma	III	Hartmann's procedure	Ureterocutaneostomy
22	48	F	Lower rectum	Well differentiated adenocarcinoma	III	Anterior resection	Ileal conduit
23	57	M	Lower rectum	Moderately differentiated adenocarcinoma	III	APR	Ileal conduit
24	47	F	Ascending colon	Moderately differentiated adenocarcinoma	III	Right hemicolectomy	Ileal conduit
25	50	F	Lower rectum	Moderately differentiated adenocarcinoma	III	APR	Ileal conduit
26	51	F	Lower rectum	Moderately differentiated adenocarcinoma	III	APR	Ileal conduit

APR, abdominoperineal resection

Table 3 Invasion of adjacent organs

Primary disease	
Bladder	3 (2)
Bladder and seminal vesicle	2 (1)
Bladder and ureter	1
Bladder and vagina	1
Bladder, seminal vesicle and prostate	6
Bladder, ureter, seminal vesicle and sacrum	1
Bladder, uterus, vagina and perineal skin	1
Seminal vesicle and prostate	2 (1)
Recurrent disease	
Bladder and ureter	2
Bladder and uterus	1
Bladder and vagina	1
Bladder, vagina and pelvis	1
Bladder and pelvis	1
Bladder, ileum, ureter and pelvis	1
Bladder, ureter, vagina, pelvis and sacrum	1
Bladder, uterus, vagina and pelvis	1

Values in parentheses are patients with no histological evidence of invasion despite surgical findings

complications. One, who had also received radiotherapy for cervical carcinoma 17 years previously, developed an ileoperineal fistula secondary to ileoileal anastomotic dehiscence. This was successfully managed conservatively. Postoperative ileus and upper gastrointestinal bleeding developed in one patient each; both were successfully treated without operation. The remaining patient had massive intraoperative bleeding (30 litres) and died from multiple organ failure associated with ureteroileal and ileoileal anastomotic leakage 26 days after operation.

Stage II primary disease

The 5- and 10-year survival rates in this group were both 71 per cent and the mean survival time was 58 (range 16–135) months (*Fig. 1*). All seven patients received potentially curative surgery. Three died from recurrence: one from liver metastases and two from pelvic recurrence with liver metastases. A further patient died from heart failure. Three patients are presently alive and disease-free.

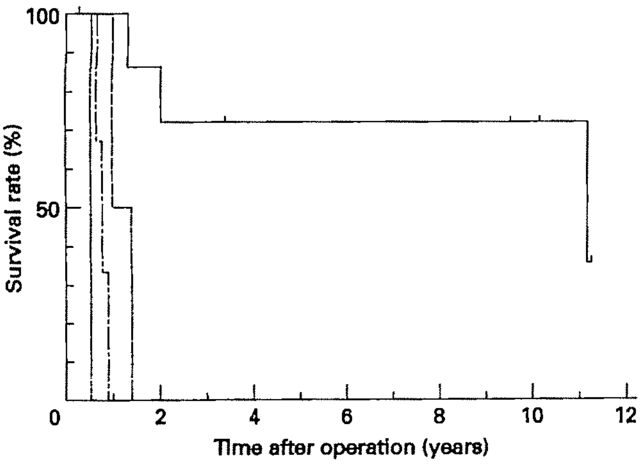

Fig. 1 Survival of patients with primary colorectal cancer according to stage. ——, Stage II; – – –, stage III (curative surgery); ——·——, stage III (non-curative surgery); - - - - - - -, stage IV. A significant difference ($P < 0.05$, log rank test) was found between patients with stage II and both stage III (curative or non-curative) and stage IV primary disease. No significant difference was found in stage III primary disease between curative and non-curative surgery

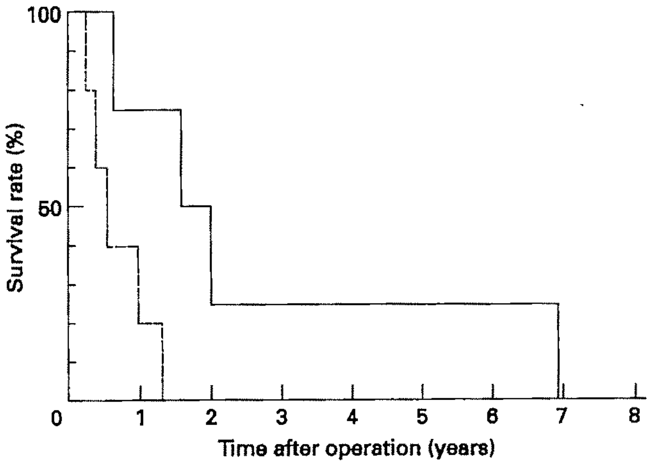

Fig. 2 Survival of patients with recurrent colorectal cancer. ——, Curative surgery; – – –, non-curative surgery. A significant difference was found ($P < 0.05$, log rank test)

Stage III primary disease

Five of these eight patients underwent potentially curative surgery. Four died from recurrence within 17 months, with a mean survival time of 14 (range 12–17) months. One died with liver metastases, one from pelvic recurrence plus liver metastases, one from liver metastases plus peritoneal dissemination and one from pelvic recurrence plus liver and lung metastases. The fifth patient died from pelvic sepsis 20 days after operation. Three patients received non-curative surgery because of para-aortic lymph node metastasis, or residual tumour in the lateral pelvic wall. All died from recurrence or metastases within 1 year, with a mean survival time of 9 (range 8–11) months (*Fig. 1*).

Stage IV primary disease

These two patients underwent total pelvic exenteration; both had distant metastases. Both died from recurrence within 7 months with a mean survival time of 5 months.

Recurrent disease

Four of the nine patients with recurrent disease underwent potentially curative surgery. Three subsequently died from pelvic recurrence and one from liver metastases. The 5-year survival rate was 25 per cent and the mean survival time 33 (range 8–83) months (*Fig. 2*). Five patients received non-curative surgery; one had liver metastases, two had lung metastases plus peritoneal dissemination and one had residual tumour in the pelvic side wall. Four died from recurrent carcinoma within 16 months, at a mean of 10 (range 5–16) months. The remaining patient died from multiple organ failure 26 days after operation.

Discussion

Total pelvic exenteration for locally advanced pelvic cancer was first reported by Brunschwig[13] in 1948. This procedure is an option for primary or recurrent disease, but carries high morbidity and mortality rates[6,14–19]. Good results are obtained in some cases because the pelvic mass or tumour adhesions to adjacent organs can be inflammatory rather than neoplastic. Therefore, patient selection is extremely important. Diagnostic techniques such as CT, MRI and endoluminal ultrasonography proved extremely useful for staging, together with preoperative or intraoperative tumour biopsy for histological diagnosis. In the present series tumour invasion was detected at higher rates (76 per cent for primary disease, 100 per cent for recurrent disease) than in previous reports (33–74 per cent)[1,3,4,20,21].

Pelvic exenteration is associated with considerable postoperative morbidity and mortality, although reporting criteria vary among authors. Previous studies report morbidity rates between 26 and 100 per cent[6,14–19]. In the present series, major complications developed after 24 per cent of operations for primary disease and 44 per cent of those for recurrent disease. Anastomotic dehiscence caused by damage following radiotherapy for cervical cancer frequently occurs, as reported by Lopez *et al.*[15]. Major complications occur at a higher rate in patients with recurrent disease because of the extent of surgery, unexpectedly wide tumour spread or uncontrolled massive bleeding. The present operative mortality rate was 8 per cent, similar to values in recent reports[6,15,16]. This might be reduced by improved preoperative planning and postoperative management. Most patients who developed severe complications recovered with conservative treatment. Postoperative quality of life in patients who underwent curative surgery was excellent and many returned to work.

Survival rates at 5 years of between 32 and 79 per cent have been reported after radical pelvic exenteration[1–5]. The survival rate is higher in patients with stage II disease[15,16,19,22], in whom the biological malignancy of the tumour appears to be lower. The tumour in these patients, despite its size, appears to remain confined to the pelvis, with no metastatic spread. However, local recurrence may derive from intraoperative tumour implantation or from occult tumour cells within pelvic lymphatics or veins. It is doubtful whether pelvic exenteration is of benefit for patients with stage III or IV disease because of their short survival. However, the management of pelvic recurrence is difficult and pelvic exenteration is effective in controlling local symptoms and may provide good palliation in a few selected patients.

Lindsey *et al.*[19] reported that a palliative exenteration provided symptomatic relief and improved quality of life for many patients; however, Boey *et al.*[16] found that incomplete resection afforded only transient palliation. In the present series, survival was short for those who had palliative surgery and the operation has little or no role in these cases.

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Cell proliferation kinetics are abnormal in transitional mucosa adjacent to colorectal carcinoma

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The transitional mucosa adjacent to colorectal carcinoma shows characteristic morphological and histochemical abnormalities that may be indicative of premalignant changes. Sixteen colorectal carcinomas were studied to analyse the proliferative activity and its distribution pattern in tissue samples from transitional mucosa located within 2 cm of the cancer and from uninvolved mucosa 10 cm from the cancer. Proliferative activity was assessed using a monoclonal antibody to proliferating cell nuclear antigen (PCNA). The total labelling index (percentage of labelled cells in a column) of transitional mucosa was not significantly different from that of uninvolved mucosa and normal control mucosa but it was significantly higher in cancer tissue ($P < 0.001$). An upward shift of the compartment of proliferating epithelial cells towards the bowel lumen was seen in transitional mucosa. The labelling index of the middle compartment (compartment 3) of the crypt in transitional mucosa was significantly higher than that in uninvolved mucosa and control mucosa ($P < 0.001$). Unstable cytokinetic change may already have started in apparently normal transitional mucosa. Assessment of cell proliferation kinetics by PCNA immunostaining may be useful in screening for heightened risk of the development of colorectal cancer.

The mucosa adjacent to colorectal carcinomas is histologically normal but has altered mucous secretions[1–3]. The term transitional mucosa was first used by Filipe in 1969[1] to indicate the mucosa surrounding a colorectal adenocarcinoma. Transitional mucosa shows a significant increase in non-sulphated sialomucin, in contrast to normal colonic epithelium in which sulphomucin predominates; it has morphological, ultrastructural, biochemical, and histochemical abnormalities mimicking those of tumours[2–5]. These findings have led to the suggestion that transitional mucosa has already undergone specific premalignant changes, and perhaps has reverted to a more primitive state. However, not all studies agree with this hypothesis; some investigators have suggested that such changes are secondary to the presence of the nearby carcinoma[6–8].

Previous studies have shown an inverse correlation between the length of transitional mucosa around locally invasive (Dukes B) carcinomas and survival[9], and a close correlation between the transitional mucosa retained at the resection margins and a poorer prognosis[10,11]. The evaluation of surgical resection margins by differential mucin staining is reliable for predicting synchronous and metachronous colorectal carcinoma[12]. In addition, the deep branching crypts of transitional mucosa show similar morphological alterations in rodents treated with carcinogens[13].

Only a few studies on cell proliferation kinetics in transitional mucosa have been reported[14–16]. In the present study, cell proliferation kinetics in transitional mucosa and uninvolved mucosa were investigated by immunostaining for proliferating cell nuclear antigen (PCNA).

Patients and methods

Endoscopic biopsies of rectal wall mucosa were obtained from six control patients with a negative personal and family history of colorectal neoplasia. Tissue samples were obtained from 16 unselected patients who had operations for colorectal carcinoma in this department between January and December 1992. Samples of cancer tissue, transitional mucosa and uninvolved mucosa were obtained from each patient. The transitional mucosa specimens were taken within 2 cm of the cancer and the specimens of uninvolved mucosa were obtained at least 10 cm from the cancer. The patients included eight men and eight women with a mean age of 62 (range 38–70) years. By Dukes classification, six were stage A, five were stage B and five were stage C. By histological grade, 11 showed well differentiated and five moderately differentiated carcinoma. All tissue samples were removed within 1 h of resection and immediately fixed in formalin. The samples were then processed with conventional procedures for paraffin embedding.

Immunohistochemistry of cell kinetics

Paraffin sections, 3-μm thick, were mounted on glass slides coated with poly-L-lysine and air dried overnight at room temperature. The sections were deparaffinized in xylene, hydrated through a graded alcohol series and immersed in methanol containing 3 per cent hydrogen peroxidase to block endogenous peroxidase activity. Normal rabbit serum was applied for 30 min to reduce non-specific antibody binding. The sections were then immunostained by the avidin–biotin complex method. They were incubated for 1 h at room temperature with an anti-PCNA antibody (PC 10; Novocastra Laboratories, Newcastle upon Tyne, UK) at a 1 : 200 dilution. The slides were developed with 3,3'-diaminobenzidine tetrahydrochloride solution containing 0·1 per cent hydrogen peroxide and were lightly counterstained with haematoxylin. Normal mouse immunoglobulin was substituted for primary antibody as the negative control.

Immunohistological examination

Mucosa adjacent to, and overlying, tumours was initially examined to identify morphological features of transitional mucosa, including irregular, branched crypts containing enlarged goblet cells (*Fig. 1*)[2]. Attention was mainly confined to longitudinally oriented crypts visible along their entire length. Assessment of the labelling index and distribution of cells with PCNA expression was carried out by dividing columns into five compartments longitudinally from the base (no. 1) to the luminal surface (no. 5) of the crypt[17]. The labelling index was defined as the percentage of cells stained positive for PCNA in each

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compartment. Labelling indices were each measured in at least 15 crypts in between five and eight randomly chosen microscopic fields. In cancer tissue, few full-length crypts were seen because of their tortuous course; 1000 cells were therefore observed at random and counted. The sections were examined using a × 400 objective with an IBAS 20 computer image analysis system (Zeiss, Oberkochen, Germany), which is capable of identifying and counting positive cells with a designated optical density. It has sensing channels at 620 nm and 500 nm, one of which identifies all the components counterstained with haematoxylin and the other the nuclear components stained immunohistochemically. All assessments were performed by a single observer without knowledge of pathological or surgical data.

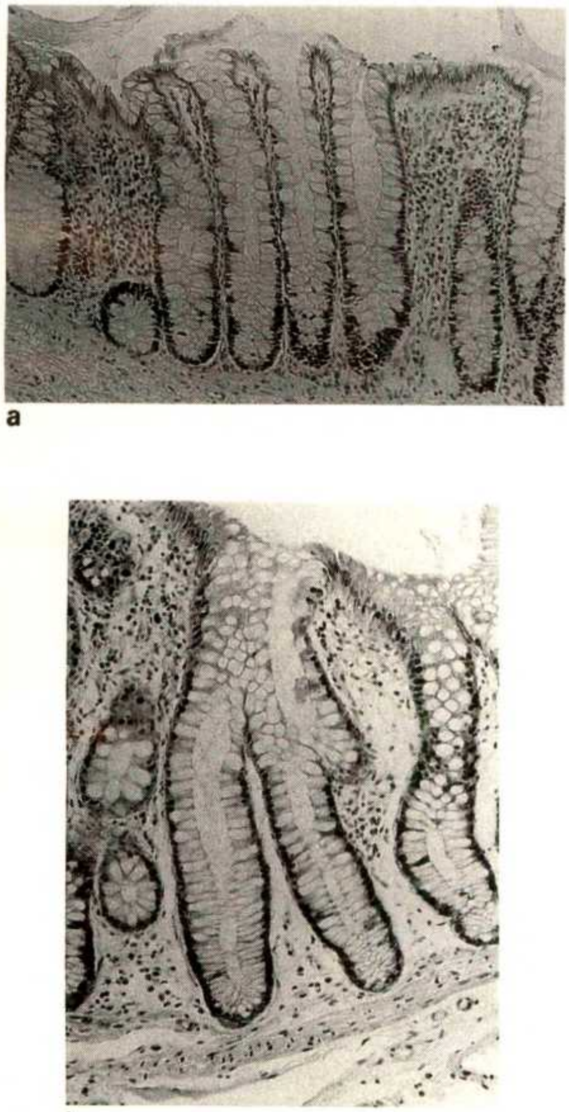

Fig. 1 **a** Normal colonic mucosa. Proliferating cell nuclear antigen (PCNA)-positive cells with dark stained nuclei are only observed in the lower three-fifths of the crypts. **b** Transitional mucosa adjacent to colorectal carcinoma. PCNA-positive cells show upward migration toward the luminal surface. Note the increased mucosal thickness, complex branching of the crypts, and goblet cell hyperplasia. (Haematoxylin, original magnification × 100)

Statistical analysis

Results are expressed as mean(s.d.). Comparisons between the mean cell kinetic values were performed primarily using Student's *t* test for unpaired data. When the distribution of the data was skewed, the results were evaluated with the non-parametric Mann–Whitney *U* test. Differences were considered significant at $P<0{\cdot}05$.

Results

Proliferative activity

The mean(s.d.) total labelling index of the rectal mucosa in control subjects was 13·7(3·7) (range 7·7–17·0) per cent. In patients with cancer, the mean(s.d.) total labelling index of uninvolved mucosa was 12·3(2·8) (range 9·3–18·0) per cent and that of transitional mucosa was 14·4(2·8) (range 10·3–19·4) per cent (*Fig. 2*). There was no significant difference between normal control mucosa *versus* uninvolved mucosa ($P=0{\cdot}33$), normal control mucosa *versus* transitional mucosa ($P=0{\cdot}64$), and uninvolved mucosa *versus* transitional mucosa ($P=0{\cdot}34$).

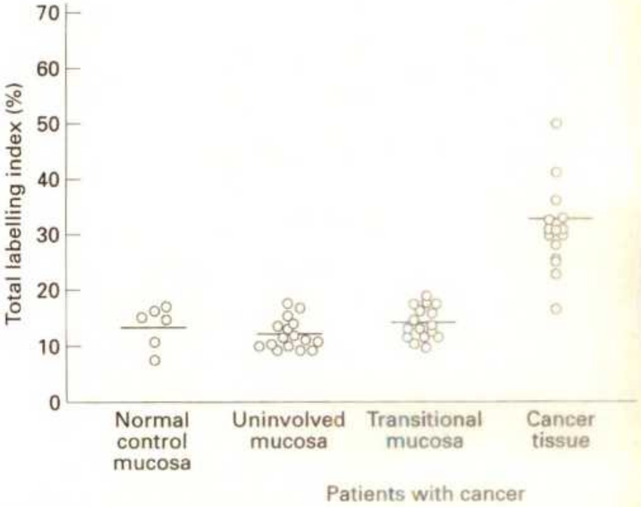

Fig. 2 Total labelling index of normal control mucosa, uninvolved mucosa, transitional mucosa, and cancer tissue. Individual values are shown and bars represent the mean

Table 1 Distribution of individual crypt compartment epithelial cell proliferation in transitional mucosa, uninvolved mucosa and normal control mucosa

	No. of labelled cells/total no. of cells (labelling index) in each compartment		
	Normal control mucosa	Uninvolved mucosa	Transitional mucosa
Compartment 1 (base)	829/2390 (34·7)*	762/2450 (31·1)	560/2050 (27·3)
Compartment 2	680/2428 (28·0)	535/2415 (21·3)	542/2110 (25·7)
Compartment 3	1441/2448 (5·9)†	226/2534 (8·9)‡	329/2112 (15·6)
Compartment 4	0/2420 (0)	0/2510 (0)	76/2108 (3·6)
Compartment 5 (lumen)	0/2554 (0)	0/2664 (0)	0/2180 (0)

*$P<0{\cdot}05$ (normal control mucosa *versus* transitional mucosa); †$P<0{\cdot}001$ (normal control mucosa *versus* transitional mucosa); ‡$P<0{\cdot}001$ (uninvolved mucosa *versus* transitional mucosa); Student's *t* test for unpaired data

The mean(s.d.) total labelling index of cancer tissue was 32.9(10·5) (range 16·7–60·6) per cent, which was significantly higher than that in transitional mucosa, uninvolved mucosa, and normal control mucosa (all $P<0{\cdot}001$). There was no significant relationship between total labelling index and Dukes stage or histological differentiation.

Proliferative distribution pattern

Cells stained positive for PCNA, found only in the lower three-fifths of the crypts in both normal control and uninvolved mucosa, were defined as the proliferative zone (*Table 1*). Proliferative compartment migration towards the luminal surface was observed in transitional mucosa. There was a statistically significant difference in the labelling indices for the various compartments of the crypts between the transitional and the uninvolved mucosa. There was a greater proportion of PCNA-positive cells in the lowest crypt compartment (compartment 1) in controls than in transitional mucosa (normal control *versus* uninvolved mucosa, normal control *versus* transitional mucosa, and uninvolved *versus* transitional mucosa, $P=0{\cdot}26$; $t=2{\cdot}19$, 20 d.f., $P=0{\cdot}04$; and $P=0{\cdot}17$ respectively), but the labelling index near the crypt surface (compartment 3) was greater in transitional mucosa than in uninvolved or control mucosa (normal control *versus* uninvolved mucosa, normal control *versus* transitional mucosa, and uninvolved *versus* transitional mucosa $P=0{\cdot}18$, $P<0{\cdot}001$ and $P<0{\cdot}001$ respectively).

Discussion

It is accepted that colorectal cancers arise as a result of the accumulation of genetic alterations that disrupt the normal control of cell proliferation and differentiation[18]. The colorectal mucosa replenishes itself by cell renewal from the base of the mucosal crypts. Cells migrate to cover the surface of the crypts and are extruded from the mucosal surface.

Lipkin[19] has reported abnormal cell proliferative characteristics, including hyperproliferation and upward migration of cell proliferation in the epithelial lining, in apparently normal mucosa surrounding colon cancer using [^{3}H]thymidine. Such changes have been noted in patients with familial adenomatous polyposis (FAP)[20–23], ulcerative colitis[24–25], sporadic adenomas[26], and previous colon cancer[27]. The proliferative distribution pattern seen in transitional mucosa is consistent with a change described previously in individuals with FAP[23]. The proliferative capacity of this apparently normal flat mucosa has been reported to be similar to that of the crypts in colonic adenomas, which are considered to be precursors of cancers[28]. An increase in proliferative activity correlates with a rise in the rate of neoplastic transformation[29] and with the enlargement of adenomas[23]. *In vivo* studies of rat colon carcinogenesis have also indicated that such abnormalities are preneoplastic[30]; these changes can be seen after only a few doses of carcinogen in the mucosa both adjacent to, and remote from, the cancers.

In contrast to the present study, Lawson *et al.*[16] failed to demonstrate proliferative or enzymatic changes in transititional mucosa suggestive of a higher than expected risk for malignant change[16]. They found that crypts in the transitional mucosa had a significantly lower labelling index using the Ki 67 monoclonal antibody technique in fresh-frozen material, and there was no evidence of a shift in the proliferative zone towards the bowel lumen.

The most commonly used method of assessing cell proliferation is incubation of tissue *in vitro* with tritiated thymidine or bromodeoxyuridine (BrdU). The recent commercial availability of antibodies against PCNA has provided a simple means of identifying proliferating cells, mainly during the late G1 and S phases[31]. PCNA is an auxiliary protein of DNA polymerase delta and is essential for DNA replication[31,32]. The authors have previously demonstrated a significant correlation between the PCNA index and the BrdU labelling index[23]. In most studies the fraction of PCNA-positive cells is higher than that recorded with tritiated thymidine, BrdU, and flow cytometric DNA histograms[33]. This may, in part, be explained by the fact that PCNA expression is not a measure of replicative activity. PCNA is regulated in a complex manner with the gene being transcribed efficiently in both quiescent and proliferating cells but PCNA messenger RNA normally only accumulates in proliferating cells[34]. PCNA works in routinely processed archival tissue sections. PCNA immunostaining is an attractive method for cell proliferation analysis because of its simplicity; however, there are methodological aspects that need to be considered. PCNA expression is strongly influenced by the duration of tissue fixation; it is greatly reduced after fixation in formalin for 48 h and virtually abolished after fixation for 72 h[35]. Quantitation of PCNA immunostaining may become more objective with the use of computer image analysers. Therefore, each laboratory may have to find its own method for assessing PCNA immunoreactivity.

Although some controversies exist regarding the specificity and cause of histochemical changes in transitional mucosa supporting the premalignant hypothesis, analysis of PCNA expression still seems valuable. Normal flat mucosa is comparatively quiescent in cell proliferation. The present findings suggest that the upward shift of the compartment of proliferating epithelial cells towards the bowel lumen in transitional mucosa may characterize the region with a higher than expected risk for neoplastic transformation. This appears to be an early and persistent event in the adenoma–carcinoma sequence, and may itself further contribute to the abnormal cell development necessary for malignant change. There are potential screening opportunities although more analysis and confirmatory studies are needed.

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Short note

Randomized trial of fibrin glue to seal mechanical oesophagojejunal anastomosis

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This study assessed the effect of reinforcing fibrin glue on the anastomotic leak rate after mechanical oesophageal anastomosis.

Patients and methods

Over 6 years, 86 patients having total gastrectomy for gastric adenocarcinoma were randomly divided to reinforcement of the anastomosis with fibrin glue (42 patients) or to a control group (44).

For curative resection (26 patients with fibrin glue, 29 without), the excision technique included R_2 gastrectomy. An extended procedure was performed in 53 patients. End-to-side oesophagojejunal stapled anastomosis was performed on all patients using a Roux-en-Y jejunal loop, forming the tobacco pouch of the oesophagus manually. During approximation of the anvil to the staple cartridge, fibrin glue (Tissucol; Immuno AG, Vienna, Austria) was applied to both surfaces[1]. No other reinforcing sutures were used.

On day 7 after operation the anastomosis was checked by contrast radiography. Two types of fistula were identified, according to Csendes' classification[2]: type I – local fistula, with no leak through a fistulous track to the pleural or abdominal cavity, or the appearance of contrast material in any abdominal drain; type II – leakage into the pleural or abdominal cavity, with appearance of the contrast medium in any of the abdominal drains.

The χ^2 test with the Yates' correction and the t test were used for statistical analysis.

Results

The clinical details are shown in *Table 1*. There were no deaths in hospital. There were four fistulas in the control group of patients, three type I and one type II, but none in the group that received fibrin glue. However, a statistically significant difference was not found. None of the patients with a leak had suffered perioperative hypotension, hypoxia or sepsis. In all four patients the preoperative serum albumin level was in excess of 35 g/l. None of the fistulas required repeat surgery; all resolved with the administration of parenteral nutrition.

There were three late anastomotic stenoses, none owing to tumour relapse. Two were found in patients treated with fibrin glue. The stenosis in the control group occurred in a patient with a type II leak. All were satisfactorily treated by endoscopic dilatation.

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Table 1 Clinical details

	With fibrin glue ($n = 42$)	Without fibrin glue ($n = 44$)
Median (range) age (years)	66 (34–85)	64 (41–83)
Sex ratio (M : F)	33 : 9	33 : 11
Concomitant disease*	18	17
TNM stage		
I	6	7
II	7	10
III	16	21
IV	13	6
Additional operative procedure		
Splenectomy	22	26
Tail of pancreas resection	12	12
Liver resection	3	1
Duodenopancreatectomy	2	0
Colonic resection	5	2
Diaphragmatic resection	0	1
Postoperative complications		
Respiratory infection	1	3
Pulmonary embolism	1	1
Subphrenic abscess	1	1
Duodenal disruption	1	1
Subclavian thrombosis	0	2
Pancreatic fistula	0	2
Colonic fistula	0	1
Jejunal volvulus	0	1
Median (range) length of hospital stay (days)	17 (11–34)	23 (10–61)†
Late anastomotic stricture	2	1
Leak		
Type I	0	3
Type II	0	1

*Includes diabetes mellitus, lung disease, coronary artery disease, obesity and high blood pressure. TNM, tumour node metastasis. †$t = 2{\cdot}2$, 59 d.f., $P = 0{\cdot}03$

Discussion

Various clinical studies have made positive assessments of fibrin adhesives in achieving a greater degree of sealing in high-risk anastomoses[3], although so far a prospective randomized clinical trial has not been performed.

In experimental surgery the results are contradictory: some studies show that fibrin sealing contributes favourably to anastomotic healing[4], whereas others refute this effect[5].

In this study hospital stay was longer ($P = 0{\cdot}03$) in patients in whom biological glue was not used, but this depended largely on factors unconnected with anastomotic dehiscence or leaks.

This study has shown that the application of fibrin glue to oesophagojejunal anastomoses could have a favourable effect in reducing anastomotic dehiscence, although this result was not statistically significant because of the small number of patients studied. The incidence of oesophagojejunal anastomotic leakage is normally less than 5 per cent, so it would have been necessary to study at least five times the number of patients in the present series to show a positive effect of fibrin glue. These results justify the need to carry out multicentre research on this question.

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Multicentre study of surgical complications of colonoscopy

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A total of 196 records of colonoscopic surgical complications were reviewed during a 12-year period. Perforation (183 patients) and haemorrhage (11) were the two main complications. Diagnosis of perforation was delayed in 58 per cent of patients. The sigmoid colon was the site of perforation in 72 per cent with evidence of peritoneal contamination in 59 per cent. Postoperative mortality rate of perforation was 12 per cent and was significantly related to a past history of medical disease and size of perforation. Postoperative morbidity rate was 43 per cent. There were two deaths after colostomy closure. The overall mortality rate of colonoscopic perforation requiring an emergency surgical procedure reached 14 per cent. Haemorrhage always occurred after endoscopic polypectomy; the postoperative course was uneventful in these patients.

Colonoscopy is a diagnostic and therapeutic procedure with a complication rate ranging from 0·1 to 0·8 per cent for perforation[1,2] and from 0·4 to 1 per cent for haemorrhage[3–6]. This rate increases to 3 per cent when endoscopic polypectomy is performed[1]. Few data are available concerning the surgical treatment of these complications and associated morbidity and mortality rates.

To evaluate the colonoscopic complications requiring emergency surgery a retrospective multicentre study of 196 patients was carried out.

Patients and methods

In July 1992, the French Associations for Surgical Research sent a questionnare requesting information on surgical complications of colonoscopy to all members of these Associations and members of the French Society of Digestive Surgery A total of 196 records of patients operated on for colonoscopic complications during a 12-year period (1981–1993) were collected from 54 centres. Information collected included: past medical history, indication for endoscopy, type of endoscopy (diagnostic or therapeutic), characteristics of the complications, type of peritonitis, diagnosis and surgical timing and precise type of surgical procedure and postoperative mortality and morbidity rates. Results are presented as mean(s d.).

Results

There were 111 men and 85 women with a mean(s.d.) age of 67(12) years. There were 183 perforations (93 per cent) and other complications were: haemorrhage (11 patients), splenic trauma (one) and diathermy snare entrapment (one). Only perforation and haemorrhage were analysed in the present study.

Perforations

There were 104 men and 79 women with perforations (mean(s.d.) age 67(12), range 25–91 years) and 80 (44 per cent) were older than 70 years. A past history of medical disease was present in 53 patients (31 per cent). Indications for colonoscopy are listed in *Table 1*. Sixty-eight patients (38 per cent) underwent a therapeutic endoscopy (*Table 2*).

Table 1 Perforations· indications for colonoscopy

Indications for colonoscopy	*n*
Functional disorders	89
Haemorrhage	28
Known polyp	26
Anaemia	10
Ulcerative colitis	7
Cancer	4
Miscellaneous	5
No information	14

Table 2 Perforations· details of 'therapeutic' colonoscopies

'Therapeutic' colonoscopy	*n*
Polypectomy	51
Biopsy	6
Laser	5
Dilatation	2
Colonic decompression	2
Tumour resection	1
Photocoagulation of angioma	1
Total	68

Table 3 Site of perforation

Site of perforation	*n*
Rectum	12
Sigmoid	132
Left colon	15
Transverse colon	6
Right colon	15
Small bowel	2*
No perforation found	2

*One patient had a perforation of both right colon and small bowel

Diagnosis of perforation was immediate in 75 patients (42 per cent) and delayed in 100 (58 per cent), from 1 h to 42 days after colonoscopy.

Clinical signs were noted in 146 patients: 76 had peritonitis, 55 isolated pain, five had septic shock, three developed general signs of sepsis, one had rectal bleeding

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Table 4 Perforations: details of surgical procedure

Surgical treatment	*n*	Colostomy (*n*)
Simple closure	59 (32)	20
Resection without suture	48 (26)	48
Resection with suture	40 (22)	5
Exteriorization of perforation	33 (18)	33
Miscellaneous	3 (2)	2

Values in parentheses are percentages

Table 5 Perforations: details of postoperative surgical complications

Surgical complications	*n*	Reoperations
Wound complication	25	7
Wound infection	17	1
Wound dehiscence	7	5
Other	1	1
Stomal complication	3	0
Colostomy prolapse	2	0
Peristomal evisceration	1	0
Intraperitonal abscess	8	7
Fistula	5	3
Colonic fistula	4	2
Small bowel fistula	1	1
Postoperative haemorrhage	2	2
Small bowel obstruction	3	2
Miscellaneous	3	3

and six miscellaneous.

Plain abdominal radiographs were performed in 139 patients and showed pneumoperitoneum in 116 (84 per cent), retropneumoperitoneum in six (4 per cent) and were normal in 17 (12 per cent). Contrast media enema was performed in four patients, two of whom had a pneumoperitoneum on plain abdominal radiograph.

Delay between perforation and surgical intervention was recorded in 175 patients. Mean delay was 30 h and 48 per cent of the patients were operated on less than 6 h after endoscopy, 13 per cent more than 48 h after.

Anatomic lesions. Sites of perforation are listed in *Table 3*. The size of perforation was measured in 149 patients and found to be less than 2 cm in 73 (49 per cent) and more than 2 cm in 76 (51 per cent). Peritonitis was present in 108 patients (59 per cent) and 72 had no evidence of peritoneal infection at laparotomy (39 per cent). Two patients had a retroperitoneal abscess. Peritonitis was more frequent in patients operated on more than 6 h after perforation (76 *versus* 43 per cent).

Surgical procedure. Surgical procedures are listed in *Table 4*. Simple closure of the perforation was carried out more frequently in the absence of peritonitis (44 *versus* 25 per cent) and when operation was performed within 24 h of perforation (28 *versus* 14 per cent). Hartmann's procedure and resection without anastomosis was carried out more frequently in patients operated on after 48 h (52 *versus* 22 per cent).

A defunctioning colostomy was performed in 108 patients (59 per cent), especially if there was peritonitis (71 *versus* 39 per cent), and a delay of more than 12 h (76 *versus* 47 per cent).

Postoperative course. Information concerning the postoperative mortality rate was available in 181 patients. Twenty-two patients (12 per cent) died in the postoperative period and the mortality rate was higher in those with underlying medical disease (29 *versus* 4 per cent) and when the size of the perforation was more than 2 cm (21 *versus* 1 per cent). Mortality rate was not influenced by age, type of colonoscopy (diagnostic or therapeutic), delay of diagnosis, timing and type of the surgical procedure, location of perforation or peritoneal infection.

Postoperative complications occurred in 77 patients (42 per cent). There were 44 medical and 42 surgical complications requiring 23 reoperations (*Table 5*). Morbidity rate was higher in those with pre-existing medical disease (62 *versus* 31 per cent) and when colonic resection was performed (50 *versus* 38 per cent), but it was not influenced by age, type of colonoscopy (diagnostic or therapeutic), delay of diagnosis, timing and type of surgical procedure, location of perforation or peritoneal infection.

Long term follow-up. Seventy-nine of the 96 patients (83 per cent) treated by colostomy underwent colostomy closure with a mean delay of 4 months. Morbidity and mortality related to this second operation were respectively 21 per cent and 3 per cent (two patients). Two deaths occurred after colorectal anastomoses in patients with a Hartmann's procedure.

The overall mortality rate of colonoscopic perforation requiring an emergency surgical procedure was 14 per cent.

Haemorrhage

There were six women and five men with haemorrhage who had a mean(s.d.) age of 66(16) years and all underwent a therapeutic endoscopy for polypectomy. Diagnosis of haemorrhage was immediate in seven and delayed in four, 2, 3, 4 and 12 h after endoscopy respectively. In all patients, the location of haemorrhage was at the site of polypectomy.

Surgical haemostasis was made by colotomy and simple suture in seven patients and colonic resection with anastomosis in four. The postoperative course was uneventful in all patients.

Discussion

The reported complication rate of colonoscopy is about 1 per cent[1–6] and the mortality rate from these complications may be as high as 50 per cent[2]. Most series report low numbers of patients[2,4,5], or include patients treated conservatively and surgically[2–7]. It is difficult to evaluate the results of surgical treatment of these complications from these studies.

This retrospective survey was not exhaustive and cannot give any indication of the true incidence of complications occurring during colonoscopy.

The most frequent complications were colonic perforation (93 per cent) and haemorrhage (6 per cent) in proportions similar to other series[3].

With perforation, absence of pneumoperitoneum or retropneumoperitoneum cannot exclude the diagnosis of perforation: 14 per cent of the patients in the present series and 20 per cent in the series of Hureau *et al.*[8] had normal plain abdominal radiographs. Use of contrast media enema has been suggested in those with clinical suspicion of perforation without radiological signs on plain abdominal radiographs.

The most frequent site of perforation in this and other studies was the sigmoid colon[8,9] because of its anatomical characteristics and as it is the commonest place for polypectomy. In two patients with pneumoperitoneum, laparotomy failed to localize the site of perforation as previously described by Hall *et al.*[2].

Type of treatment was influenced by the delay between perforation and laparotomy. When surgery was undertaken more than 6 h after perforation there were less primary colonic anastomoses and a simple suture closure would be carried out in the absence of peritonitis.

Overall mortality rate of 14 per cent in this study is similar to other series (Hall *et al.*[2]: 10·8 per cent mortality rate in a review of the literature; Hureau *et al.*[8]: 10·5 per cent, and Cuilleret[9]: 3·2 per cent). In other studies with low numbers of patients, the mortality rate ranged from 0 to 55 per cent.

Mortality in this study seemed to be affected by the presence of underlying disease and by the size of perforation, and these two factors have been previously described as risk factors[10–14].

Closure of a defunctioning colostomy increased the overall mortality rate from 12 to 14 per cent and clearly, surgery should be undertaken as soon as the diagnosis of perforation has been made.

Conservative treatment is most frequent[3,4,6,15] for haemorrhage but emergency surgery is required in up to 20 per cent of patients[3,4,6,15]. In this series all haemorrhages occurred after endoscopic polypectomy and no patient died in the postoperative course.

Acknowledgements

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Short note

Failure of the unopened colostomy to protect high-risk rectal anastomoses

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Anastomotic breakdown, the most serious complication of restorative rectal resection, is responsible for half the postoperative morbidity rate and one-third of deaths[1]. While many surgeons defunction low anastomoses[2], others consider this unnecessary[3]. A tube caecostomy can be used after on-table orthograde bowel lavage to avoid a stoma[4]. An obstructing unopened loop 'colostomy' offers potential advantages[5]. It can be returned to the abdomen if the anastomosis heals soundly or opened into a colostomy if it leaks. This method was evaluated in seven patients.

Patients and methods

A convenient loop of transverse colon was exteriorized over a rod and a tube caecostomy fashioned after on-table lavage, resection and anastomosis[4]. The caecostomy was kept open by flushing twice daily and a low-residue diet was allowed once it had worked. The anastomosis was examined digitally and by a peranal water-soluble contrast study 7 days after operation. If no leak was identified and the patient's clinical condition was satisfactory, the exteriorized loop was returned to the abdominal cavity. Demonstration of a leak prompted the loop to be opened as a colostomy.

The decision to protect an anastomosis using this method was taken in seven patients. Indications included an endoanal anastomosis in one patient, acutely obstructed bowel in two, and poor blood supply, anastomotic tension, obesity, age and/or diabetes in the others.

Results

All patients had an uneventful early postoperative course and contrast studies showed no evidence of anastomotic disruption. Contrast studies demonstrated complete obstruction at the level of unopened 'colostomy' loop but all patients tolerated a low-residue diet. In all but one patient the loop was returned to the peritoneal cavity after a median of 9 (range 7–14) days.

In one patient the rod eroded the colonic loop after 14 days and required conversion to colostomy. Another patient whose loop was returned after 7 days developed colic and vomiting. Radiographs showed obstruction at the site of the returned loop which resolved after conservative treatment. Another patient whose loop was returned 9 days after operation became pyrexial with tenderness over the site of closure. A repeat contrast study suggested the possibility of a leak at the site of the loop. Following a period of conservative treatment, a further contrast study was normal and the patient recovered.

The remaining two patients developed anastomotic leaks. One leak became apparent after 36 days in a patient who had two normal contrast studies: one at 1 week after which the loop was replaced, and the second at 3 weeks when a defect was still not detectable by digital examination. The final anastomotic dehiscence became overt the day after return of the loop; no leak was revealed in a contrast study performed the previous day.

Discussion

The most important requirement for anastomotic healing is good surgical technique[1,3]. Anastomotic leakage still occurs occasionally[2,3], however, but its effects are mitigated by loop stomal diversion, particularly if the intervening colon is empty[4]. A formal stoma requires a second admission for closure with its associated risks.

An opened obstructing colonic loop[5] appeared to be an attractive means of protecting anastomoses without resorting to a temporary stoma, especially in patients with a tube caecostomy[4], as this avoids continuous gastric decompression and parenteral nutrition that are otherwise required[5]. In the present study it was not possible to reproduce the previously reported experience of a safe return of the colonic loop in 11 of 14 patients[5]. Although aware of the potential for rod erosion, daily surveillance did not anticipate its occurrence. This method has not prevented anastomotic disaster; indeed there was delayed dehiscence despite apparently normal contrast enema findings in this and the original series.

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Long-term outcome following curative surgery for malignant large bowel obstruction

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This study determined whether the long-term outcome of patients with obstructing colorectal cancer could be related to conventional pathological prognostic variables or to other clinical, operative or histological features. Ninety-eight patients with bowel obstruction who had undergone potentially curative surgery and survived the postoperative period were studied. Features related to poor long-term outcome after a median follow-up of 5 years included bowel perforation at initial operation ($P = 0{\cdot}007$), advanced tumour stage ($P < 0{\cdot}001$), poor tumour differentiation ($P = 0{\cdot}02$), mucin production by tumour ($P = 0{\cdot}004$) and the presence of vascular ($P = 0{\cdot}08$) and neural ($P = 0{\cdot}004$) invasion. Outcome was not significantly related to the seniority of the operating surgeon ($P = 0{\cdot}52$), even when this was adjusted for potentially confounding variables (adjusted hazard rate ratio for trainee surgeons 1·4 (95 per cent confidence interval 0·9–2·4), $P = 0{\cdot}16$). Conventional prognostic features may help to identify the majority of patients with obstructed colorectal cancer at high risk of tumour recurrence and death.

Acute or subacute bowel obstruction occurs in 7–47 per cent of patients with colorectal cancer[1–5] and is associated with a considerably higher postoperative mortality rate than in those without obstruction[6]. In addition to its effect on postoperative mortality, bowel obstruction may influence the outcome of affected patients who survive the postoperative period[3,7], even when those undergoing palliative surgery are excluded from analysis[1,8]. The poor long-term prognosis relative to patients without obstruction appears to be independent of potentially confounding variables such as tumour stage and histological differentiation[8,9].

It is not known whether conventional prognostic indicators are applicable to patients with obstruction, or whether they can identify individuals at high risk of tumour recurrence and death. A range of variables has been studied in a consecutive series of obstructed patients undergoing potentially curative surgery to determine whether long-term behaviour could be predicted by clinical, operative or histological features.

Patients and methods

Between 1983 and 1991, 736 patients were admitted to St Vincent's Hospital, Dublin with a diagnosis of colorectal cancer. Some 155 patients (21 per cent) presented with bowel obstruction, 98 who underwent curative surgery and survived the postoperative period formed the basis for this study. Of the 57 patients excluded, 19 had died in the postoperative period, 33 had undergone palliative procedures and for five incomplete pathological data were available. The median age of the study patients was 69 (range 44–87) years. Survival data were incomplete for four patients, who were lost to follow-up at 16, 33, 46 and 77 months. The mean length of follow-up for patients known to be alive on 1 December 1994 was 5·6 (median 5·0, range 2·9–10·3) years

Thirteen variables and their relationship with long-term survival were studied. Relevant clinical, operative and morphological data were obtained from a prospective computer database established in 1983. All pathological material for each patient was retrieved and reviewed for a range of histological features by a single pathologist, unaware of patient details or outcome.

A diagnosis of obstruction was based on clinical, radiological and operative criteria as suggested by Fielding *et al.*[10]. Postoperative mortality was defined as death occurring in hospital or within 30 days of operation. Patients were considered to have undergone curative resection if there was no evidence of residual or metastatic disease at operation and if the margins of the resection specimen were free of tumour on microscopic examination. Primary resection comprised removal of the obstructing tumour at first operation, with or without maintenance of bowel continuity. A staged resection was defined as initial bowel decompression followed by tumour resection at a later date. The left colon included the sigmoid colon, descending colon and splenic flexure.

The clinical variables included age at operation, sex and tumour site. Operative variables included the presence of concomitant bowel perforation, the seniority of the operating surgeon (consultant or trainee), the time of operation (performed as part of a routine operating list or not) and the type of operation performed (primary or staged resection). The pathological variables included the size of the obstructing cancer (maximum tumour diameter), tumour stage[11], differentiation (poor or other), type (mucinous or non-mucinous)[12], and the presence or absence of vascular or neural invasion[13].

Statistical analysis

Kaplan–Meier survival curves were constructed with cancer-related mortality as the end-point. Patients who died from causes unrelated to cancer were censored at the time of death. Differences in survival between groups were assessed by the log rank test. Two-sided P values of less than 0·05 were considered significant in all analyses. Multivariate survival analyses were performed with the Cox proportional hazards model using the Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA). Forward and backward regression models were constructed to determine variables that were independently associated with an increased risk of death. The assumptions of the proportional hazards model were checked by observing constant vertical distances over time between plots of the logarithm of the integrated hazard function for each variable[14].

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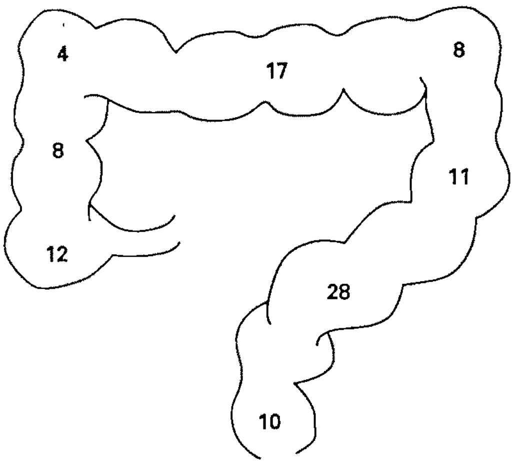

Fig. 1 Approximate site of 98 obstructing colorectal carcinomas

Results

Fig. 1 shows the anatomical position of the 98 obstructing tumours. Primary resection was performed in 92 patients. Forty-five patients underwent right hemicolectomy or an extended right hemicolectomy. A total or partial colectomy was performed in 20 patients, Hartmann's procedure in 13, anterior resection in 12 and abdominoperineal resection in two. Primary colonic decompression with delayed tumour resection was performed in the remaining six patients (two rectal, three sigmoid colon, one descending colon tumour). There was one stage A, 49 stage B and 48 stage C cancers. The single stage A tumour (a large polypoid tumour located in the sigmoid colon) was included with stage B cases for the purpose of analysis.

The median survival time of the 98 patients was 3 years and the 5-year survival rate was 35 per cent. *Table 1* shows the result of a univariate survival analysis of patients

Table 1 Univariate survival analysis and final Cox regression model of clinical and pathological features in 98 patients with malignant obstruction

		Univariate analysis		Final regression model	
	No. of patients	5-year survival rate (%)	*P*‡	Relative risk*	*P*
Age at surgery (years)†					
≤75	71	36	0·82		
>75	27	34			
Sex					
Male	52	34	0·85		
Female	46	36			
Tumour site					
Rectum	10	30	0·67		
Left colon	47	33			
Right colon	41	40			
Perforation					
Absent	85	39	0·007		
Present	13	12		3·8 (1·9–7·8)	<0·001
Surgical grade					
Consultant	56	39	0·52		
Trainee	42	28			
Operation					
Primary resection	92	36	0·91		
Staged resection	6	25			
Time of operation					
Routine list	63	39	0·67		
Out of hours	35	25			
Tumour size (cm)†					
<5	48	38	0·22		
≥5	50	33			
Tumour stage					
B	50	51	<0·001		
C	48	19		3·3 (1·9–5·8)	<0·001
Tumour type					
Non-mucinous	85	40	0·004		
Mucinous	13	0		2·3 (1·2–4·5)	0·01
Tumour differentiation					
Well or moderate	77	37	0·02		
Poor	21	26			
Vascular invasion					
Absent	79	38	0·08		
Present	19	23			
Neural invasion					
Absent	82	40	0·004		
Present	16	13			

*Values in parentheses are 95 per cent confidence intervals. †Entered into multivariate model as a continuous variable. ‡Log rank test

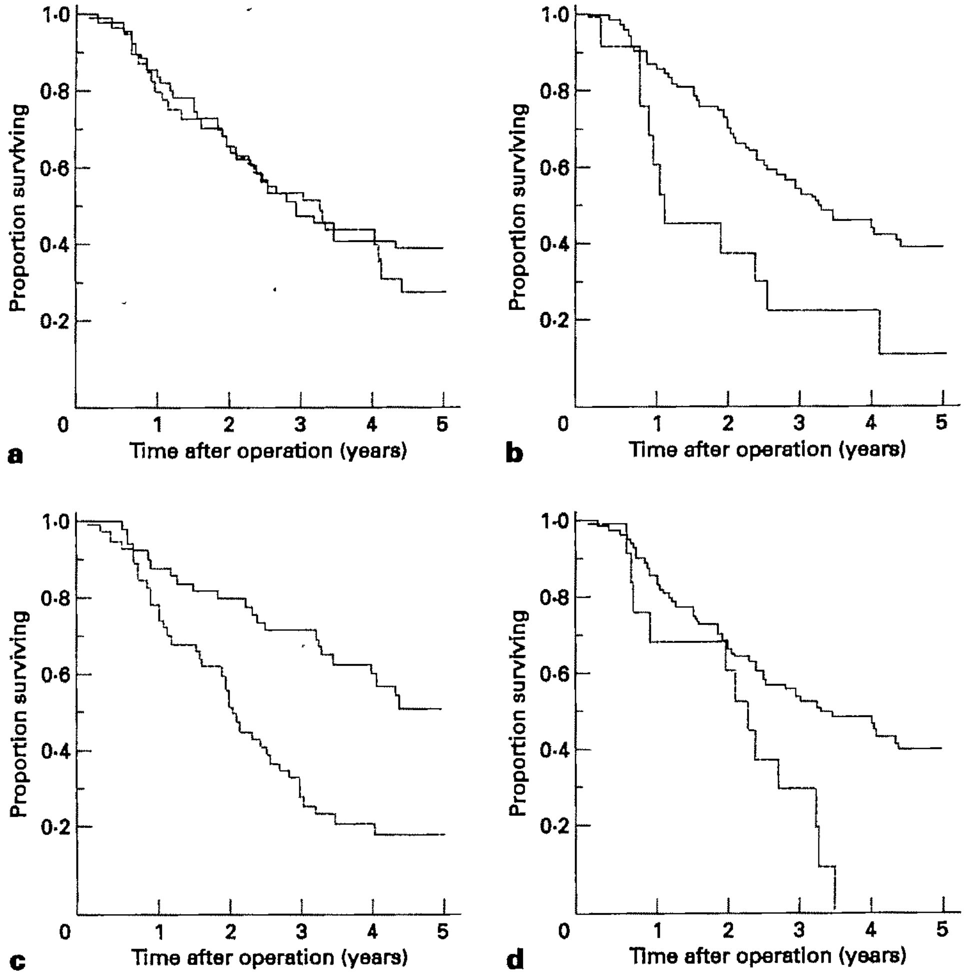

Fig. 2 Kaplan–Meier survival curves of 98 patients with large bowel obstruction stratified by a grade of operating surgeon (——, consultant ($n = 56$); ----, trainee ($n = 42$)), b presence or absence of bowel perforation (——, no perforation ($n = 85$); ----, perforation ($n = 13$)), c tumour stage (——, stage B ($n = 50$); ----, stage C ($n = 48$)) and d tumour type (——, non-mucinous ($n = 85$); ----, mucinous ($n = 13$))

Table 2 Number of operations performed by consultant and trainee surgeons involving bowel perforations, stage C tumours and mucinous tumours. The unadjusted and adjusted hazard rate ratio for trainee surgeons is also shown

	Surgical grade		
	Consultant surgeon (56 operations)	Trainee surgeon (42 operations)	*P*
Perforation			
Absent	51 (91)	34 (81)	0·14‡
Present	5 (9)	8 (19)	
Tumour stage			
B	24 (43)	26 (62)	0·06‡
C	32 (57)	16 (38)	
Tumour type			
Non-mucinous	49 (87)	36 (86)	0·79‡
Mucinous	7 (13)	6 (14)	
Relative hazard ratio†			
Unadjusted	1	1·2 (0·7–1·9)*	0·52
Adjusted	1	1·4 (0·9–2·4)*	0·16

Values in parentheses are percentages or *95 per cent confidence intervals. †Cox proportional hazards model. ‡χ^2 test

stratified into groups by clinical and operative features. The only clinical feature significantly related to outcome was the presence of bowel perforation at initial operation; only one patient in this group survived more than 5 years (*Fig. 2*). The perforation was located at the site of the tumour and associated with abscess formation in eight patients, with free perforation evident in the other five. The outlook was generally poor for patients with tumour invasion of lymph nodes, blood vessels or nerves, and for those with poorly differentiated cancer. No patient with a mucin-secreting tumour survived more than 4 years.

Forward and backward regression analysis provided the same final model, as shown in *Table 1*. The risk of death for patients with stage C tumours was relative to stage B, and the risk of death for those with mucin-producing tumours or bowel perforation was relative to those without these features. Tumour stage was the strongest prognostic feature, but the model also included bowel perforation and tumour type. Tumour differentiation, vascular and perineural invasion were excluded from the final model because of their close interaction with tumour stage.

Surgical grade was subsequently forced into the final regression model to determine the relationship between seniority of the operating surgeon and long-term outcome independent of potentially important confounding variables. *Table 2* shows the unadjusted hazard rate ratio for trainees (relative risk of death for patients operated on by trainees compared with consultants) and the hazard rate adjusted for perforation, tumour stage and tumour type. The unadjusted hazard rate ratio for trainees was 1·2, and rose to 1·4 when adjusted for perforation, tumour stage and type.

Discussion

Postoperative mortality in patients with obstructing colorectal cancer is probably related to the preoperative medical condition[2], Acute Physiology And Chronic Health Evaluation score[15], the presence of metastatic disease[6,7], bowel perforation or sepsis[7,16], operating skill[10], type of operation[6,16], and possibly patient age[3] and tumour site[16]. In contrast, the features that determine long-term survival are less clearly understood. This study therefore focused exclusively on patients who underwent curative surgery and survived the postoperative period. The results suggest that long-term outcome of individual patients with obstruction may be influenced by a number of factors, including the anatomical extent and biological activity of the primary cancer and the presence of bowel wall integrity at the time of initial surgery.

Tumour stage was an important prognostic indicator, but other histological features were also related to eventual outcome. Vascular and neural invasion have previously been found to correlate with survival following resection[9,13], while poorly differentiated and mucinous tumours are thought to represent biologically aggressive forms of disease[17,18]. All five histological features were related to outcome by univariate analysis, but differentiation, vascular and neural invasion were excluded from the final regression model because each interacted closely with tumour stage, the most powerful variable studied. Survival was less strongly related to clinical or operative variables, and the presence of concomitant bowel perforation was the only useful clinical feature studied. The combination of obstruction and perforation is thought to result in exceptionally high postoperative mortality and morbidity rates[7,16], and it is possible that the equally poor long-term prognosis of patients with a perforated tumour results from tumour cell dissemination at the time of perforation.

The National Confidential Enquiry into Perioperative Deaths[19] identified a need for more consultant involvement in patient management to optimize intraoperative and postoperative care[19]. There is also evidence that long-term outcome (without specific reference to patients with obstruction) may depend on the skill and seniority of the operating surgeon[20]. It is interesting, therefore, that the survival of patients with obstruction in this study was not greatly influenced by surgical grade. The majority of 'trainee' operations in this series were performed by senior registrars, which may have had a beneficial effect on the survival rate. The results suggest that trainees were capable of achieving adequate resection margins when attempting potentially curative resection.

Long-term outcome of patients with obstruction is related to conventional prognostic features; this finding may be useful as adjuvant therapy has been shown to improve survival in patients at high risk of tumour recurrence and death[21]. It could reasonably be argued that all patients operated on for bowel obstruction are at high risk of developing recurrent disease and should be included in trials of chemotherapy and radiotherapy. Those with additional poor prognostic features continue to provide particular treatment challenges.

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Case report

Wandering spleen: a rare emergency condition

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Wandering spleen is a rare emergency condition[1,2] in which the spleen is characterized by a long vascular pedicle, displacement from its normal position and quite often devoid of its peritoneal ligaments. It is usually asymptomatic or may present with a shifting mass in the abdomen with abdominal heaviness, vague gastrointestinal disturbance and sometimes with hypersplenism or as an emergency condition due to torsion[3].

Case report

A 12-year-old girl was admitted as an emergency complaining of acute periumbilical pain for 12 h associated with nausea and vomiting. She gave a previous history of occasional vague gastrointestinal disturbance with a feeling of abdominal heaviness. On examination a periumbilical non-shifting mass was palpated together with tenderness, rebound tenderness and guarding. The haemoglobin level was 10·9 g/dl and the white cell count $19{\cdot}2 \times 10^9$/l (86 per cent granulocytes). Emergency laparotomy was scheduled. Under anaesthetic a mobile mass could be easily palpated beneath the umbilicus. Laparotomy revealed the mass to be a wandering spleen with a 25–30-cm pedicle which was twisted anticlockwise through three revolutions. In spite of untwisting the pedicle the spleen was non-viable and splenectomy was performed together with appendicectomy. The long pedicle allowed the spleen to be delivered easily through the right paramedian incision (*Fig. 1*).

After operation the patient received pneumococcal vaccine and long-term penicillin for prophylaxis. She had an uneventful recovery and was discharged home 10 days later. Histological examination of the spleen showed haemorrhagic necrosis.

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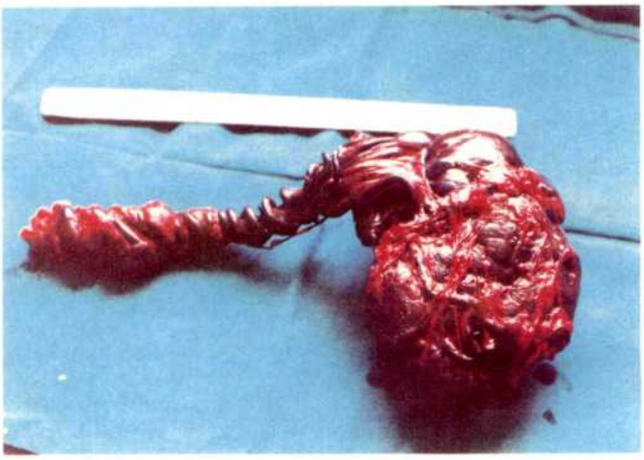

Fig. 1 The spleen after its removal

Discussion

Many theories have been suggested for the aetiology of wandering spleen including multiparity with increased abdominal laxity, splenomegaly with traction and elongation of the splenic pedicle or congenitally malformed peritoneal ligaments. Chronic or recurrent torsion may develop, causing venous congestion, splenomegaly and hypersplenism[4]. In the present case hypersplenism was absent and the cause was most probably a long pedicle with congenital absence of the peritoneal attachments. Splenectomy is the usual treatment when torsion and a non-viable spleen are present, but splenopexy is an alternative if the spleen is viable.

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Short note

Sphincter function after transanal endoscopic microsurgical excision of rectal tumours

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Benign tumours of the rectum may be destroyed by diathermy or cryotherapy, or may be locally excised using a urological resectoscope or by more invasive techniques such as the York–Mason trans-sphincteric resection[1,2]. Transanal endoscopic microsurgical excision of such tumours has the advantage of allowing a magnified view during excision, which enables resection of an unfragmented specimen with clear margins[3]. More proximal lesions can also be resected. However, the technique requires a prolonged period of anal dilatation using a 4-cm diameter sigmoidoscope, which may compromise sphincter function[4,5]. The aim of this prospective study was to examine sphincter function before and after transanal endoscopic microsurgical excision of rectal tumours.

Patients and methods

Patients undergoing transanal endoscopic microsurgical excision had anorectal manometry performed to measure maximum resting pressure, squeeze pressure and sphincter length. They were interviewed at a postoperative clinic visit and questioned about continence.

Results

Six patients had sphincter pressures and length measured before operation and at 48 h and a minimum of 6 (mean 16) weeks after operation. The mean distance of tumours from the anal verge was 9·1 (range 2–17) cm. Mean duration of surgery was 62 (range 25–90) min. Preoperative biopsy revealed adenoma in four patients and rectal cancer in two.

Resting pressure fell in five of the six patients immediately after operation to a mean of 75 per cent of the preoperative value. Squeeze pressure fell in all patients to a mean of 63 per cent of the preoperative values. The sphincter length was unchanged. At later follow-up, mean resting and squeeze pressures had both risen to the preoperative value (*Fig. 1*). Sphincter length was not changed at any time. No patient reported incontinence at a mean of 16 weeks' follow-up.

Discussion

Uncontrolled manual anal dilatation can result in episodes of incontinence in up to 27 per cent of patients undergoing the procedure[4]. This outcome may be due to disruption of the internal anal sphincter[5]. The present study has demonstrated that transanal endoscopic microsurgical excision of rectal tumours is associated with a reversible decrease in both the resting and squeeze anal pressures, which recover to preoperative values at a mean of 16 weeks after operation. The procedure does not, therefore, compromise sphincter function in the long term. Caution must be advised, however, in patients with established sphincter defects or pudendal neuropathy with

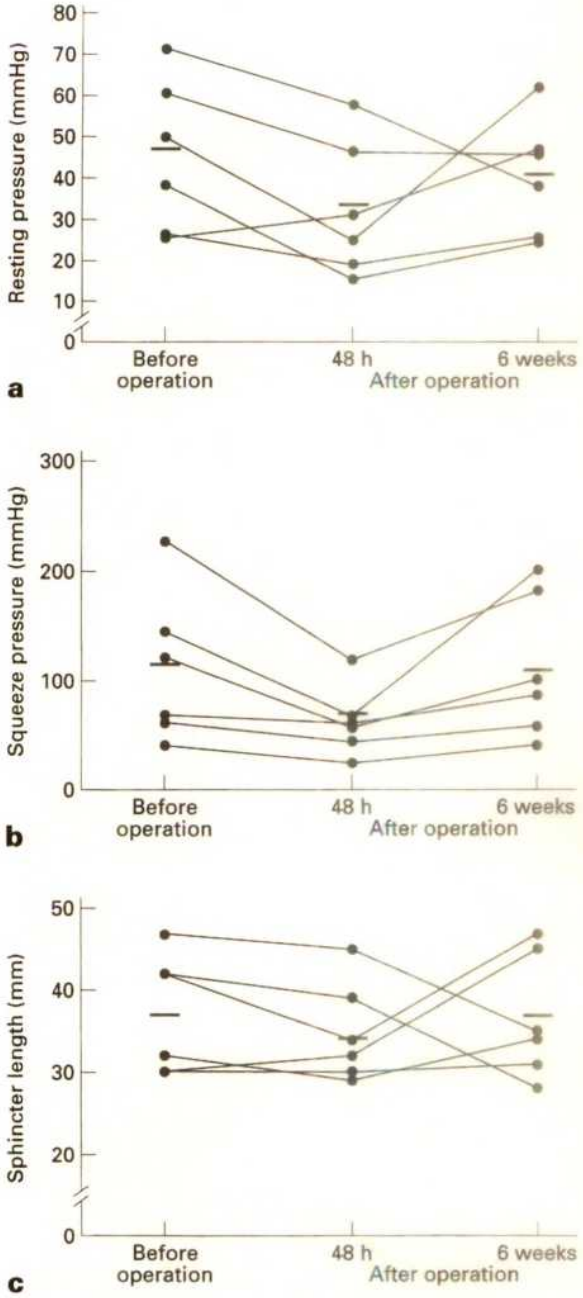

Fig. 1 **a** Resting and **b** squeeze sphincter pressures and **c** sphincter length before and after transanal endoscopic microsurgical excision of rectal tumours. Bars indicate mean value

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poor pelvic floor function, who rely on the internal sphincter alone for continence.

Transanal endoscopic microsurgical excision offers advantages over electrocautery and thermal or laser destruction in permitting either the submucosal excision of villous adenoma or potentially curative full-thickness excision of carcinoma with consequent histopathological examination of the excised specimen. Peranal local excision of rectal tumours is generally not suitable for lesions further than 8 cm from the anal margin because of inadequate access. Transanal endoscopic microsurgical excision can allow such lesions to be treated if they are on the posterior or lateral aspects of the rectum. However, caution must be expressed about the treatment of more proximal lesions, since perforation of the intraperitoneal rectum may follow excision of anterior lesions.

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Anorectal angle enhances faecal continence

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This study was performed with an *in vitro* model to assess the relative importance of sphincter pressure and anorectal angulation in maintaining faecal continence. Water and semisolid material were infused separately into porcine intestine compressed by an inflatable cuff until leakage was observed. Angulation of the bowel with respect to the cuff was 180° and then 90°. With water, holdback pressure was independent of angulation. In contrast, when semisolid material was used, angling the bowel to 90° increased holdback pressure by at least 100 per cent. Measurements taken in solid tubes demonstrated that both a restriction in the tube and an unconstricted 90° bend produced a resistance to flow of the semisolid material which was dependent on flow rate. These data suggest that liquid is retained in the rectum by occlusion pressure alone, whereas the retention of semisolid material is enhanced by angulation.

Faecal incontinence is a common socially devastating condition. Continence depends on the coordinated action of the anal sphincters (internal and external) and the pelvic floor musculature[1–5]. The sphincters produce occlusion pressure over the length of the anal canal, while the puborectalis and levator muscles produce occlusion in the upper anal canal. The puborectalis also produces angulation between the anal canal and the rectum. The presence of an acute angle at this site has been considered important in maintaining continence[6,7]. Indeed, the post-anal repair operation for idiopathic faecal incontinence was designed to correct the obtuse anorectal angle[2,8] commonly found in that condition[9,10]. More recently, the role of angulation has been questioned and occlusion pressure has been accorded the major determinant of continence[11,12]. The relative contribution of each mechanism to the maintenance of continence remains uncertain.

A fuller understanding of the mechanisms of continence is important as it may allow treatment options to be improved. To this end, the flow properties for fluid and a semisolid material in both rigid tubes and porcine bowel have been studied *in vitro* to determine the relative effects of angulation and occlusion on the resistance to flow.

Materials and methods

Study 1: Flexible tube (bowel), liquid and semisolid material

A circular inflatable cuff (75 mm long, 18 mm wide) was placed around a segment of porcine colon 16 mm wide, with a 1·5-mm wall thickness, in a manner similar to a model previously reported for studying fluid holdback[13,14]. The cuff and bowel were supported in a rigid frame so that the bowel proximal to the cuff could be placed at an angle of 180° or 90° (*Fig. 1*). The cuff was inflated to a predetermined inflation pressure and water, at a flow rate of 1 ml per min, was infused into the proximal bowel (placed at 180°) using a syringe driver. The intraluminal pressure at which water leaked through the cuffed portion of the bowel was measured by a 2-mm catheter tip transducer (Gaeltec, Skye, UK). This was repeated for a range of cuff pressures. The proximal bowel was then placed at an angle of 90° to the cuff and the holdback pressures determined as before. Semisolid material in the form of commercially produced pure collagen aqueous suspension (6 per cent collagen, 94 per cent water) was then infused into the bowel under similar conditions using a ratchet-driven injector and holdback pressures were measured. All measurements were taken three times.

The rheological characteristics of the material were evaluated using a cone and plate viscometer and found to be comparable

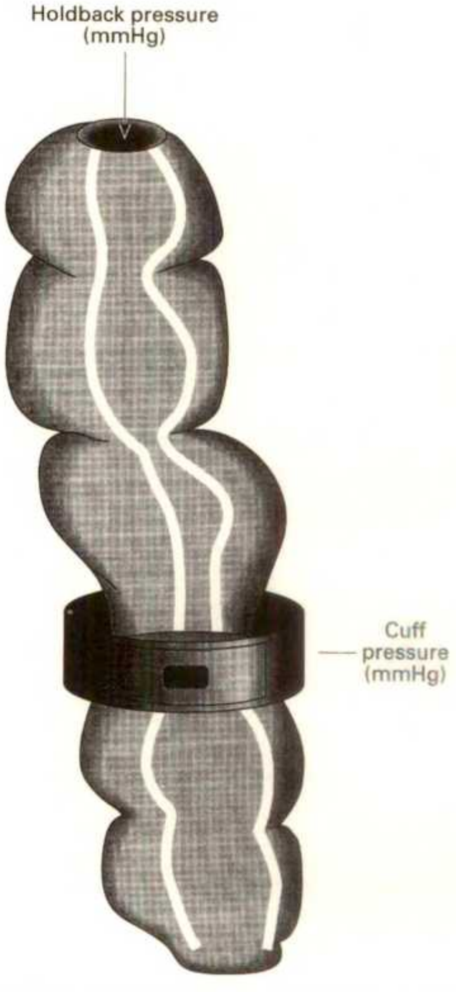

Fig. 1 *In vitro* model for measuring the retention characteristics of bowel at 90° and 180° angulation

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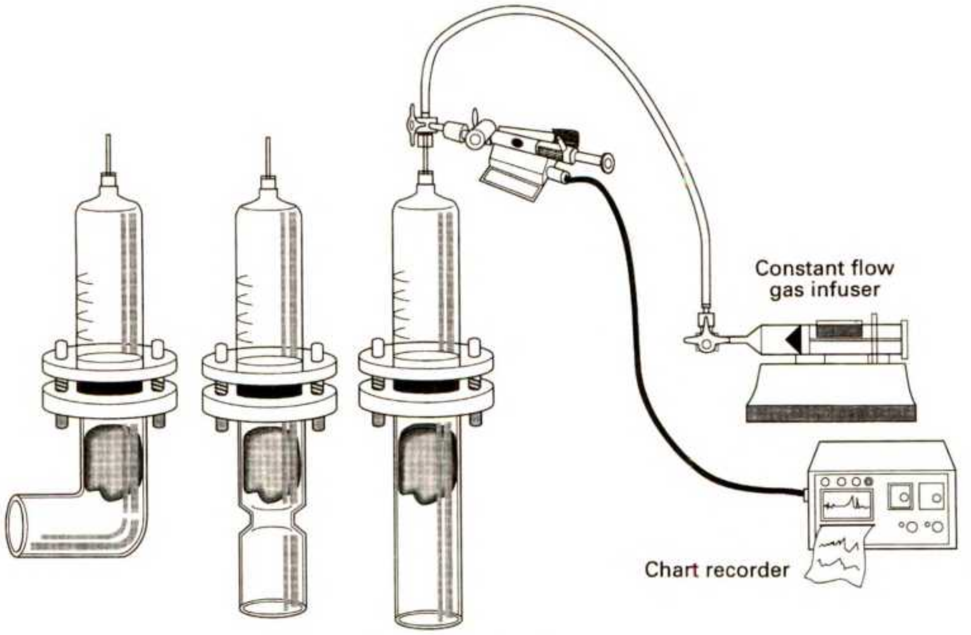

Fig. 2 Experimental set-up for studying semisolid material flow in glass tubes

to those of faeces[15] (Newtonian viscosity 280 × 10^6 kg per m per s, dynamic viscosity at 100 r.p.m. 4·9 × 10^3 kg per m per s, density 0·97 g per ml).

Colonic pressure under the cuff was assessed at each inflation pressure using the 'pull-through' technique.

Study 2: Rigid tubes, semisolid material

Three cylindrical glass tubes (diameter 28 mm) were constructed (*Fig. 2*): (a) straight, (b) straight with 50 per cent constriction and (c) 90° bend with a constant radius. A 55-mm long bolus of the collagen suspension was placed in each tube in turn. The inner surfaces of the tubes were first coated with a 1 per cent aqueous solution of hydroxypropyl-methylcellulose to simulate the lubricant properties of colonic mucus and to ensure that there was an airtight seal between the bolus and the tube. Air pressure was applied to the end of each tube using a syringe pump. The pressure when the flow of the bolus became constant was noted and the experiment was repeated at flow rates between 20 and 120 ml per min.

Results

Pressure exerted on the bowel under the cuff was directly proportional to cuff inflation pressure. The holdback pressure when water was infused into the bowel varied directly with cuff inflation pressure. There was no difference between angulation of 180° and 90° (*Fig. 3*). Semisolid material was retained at lower cuff pressures than water. At 180° there was a linear relationship between cuff and holdback pressures (r^2 = 1·00). Angulation of 90° improved retention of semisolid material by 100 per cent at low cuff pressures and by more than 300 per cent at 50 mmHg. The bowel ruptured above an intraluminal pressure of 150 mmHg (*Fig. 3*).

Flow characteristics of the semisolid material in the glass tubes are shown in *Fig. 4*. For each of the tubes, the pressure required to move the bolus increased with flow rate. The 50 per cent constriction required approximately 80 mmHg extra pressure to achieve flow whereas the 90°

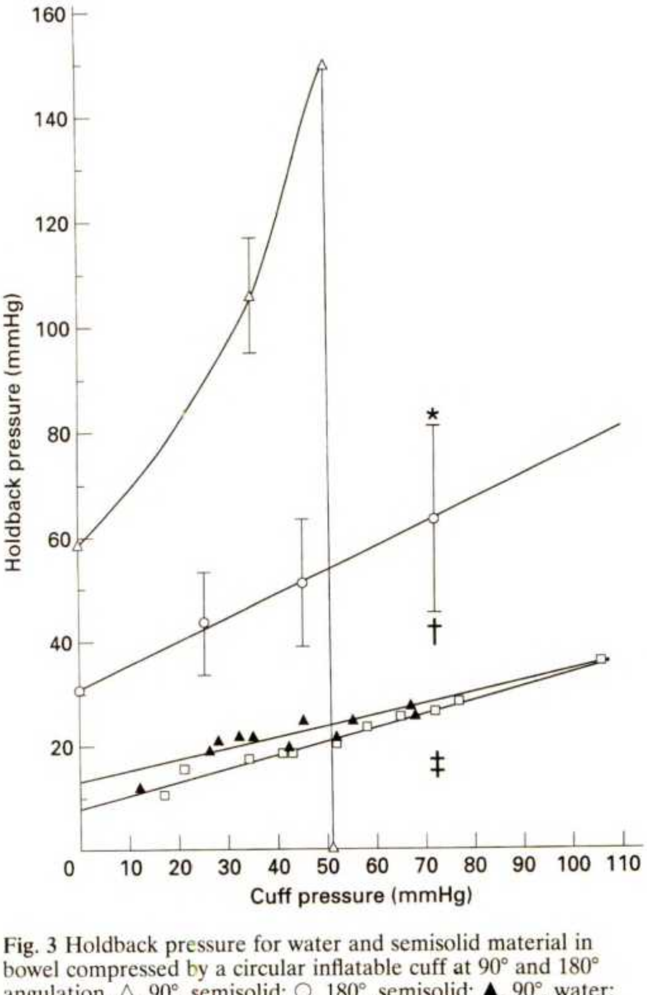

Fig. 3 Holdback pressure for water and semisolid material in bowel compressed by a circular inflatable cuff at 90° and 180° angulation. △, 90°, semisolid; ○, 180°, semisolid; ▲, 90°, water; □, 180°, water. *$y = 30{\cdot}81 + 0{\cdot}46x$ ($r^2 = 1{\cdot}00$); †$y = 13{\cdot}06 + 0{\cdot}21x$ ($r^2 = 0{\cdot}79$); ‡$y = 7{\cdot}75 + 0{\cdot}27x$ ($r^2 = 0{\cdot}98$)

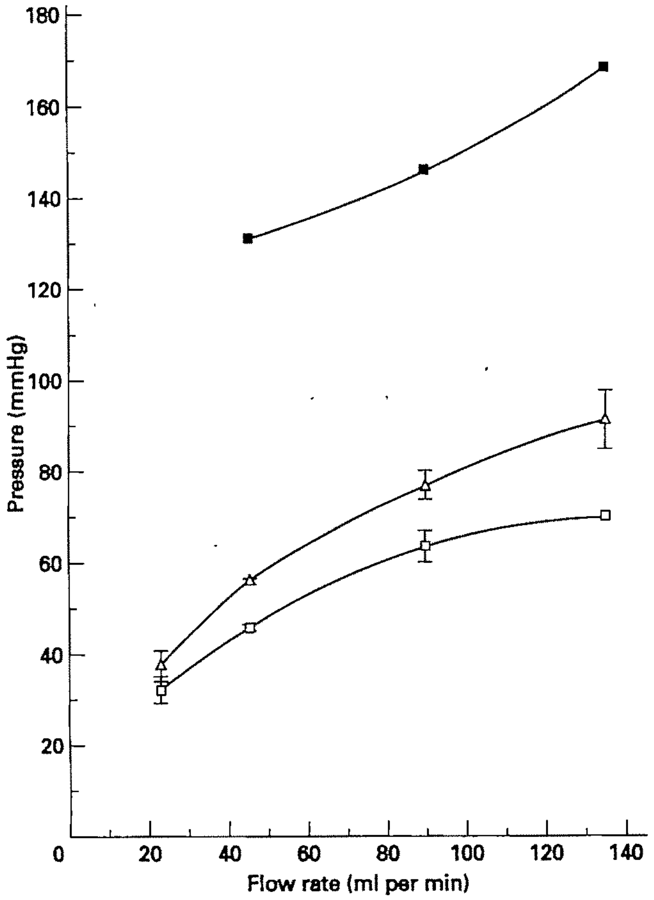

Fig. 4 Pressure to drive semisolid material through three glass tubes at different flow rates. ■, 50 per cent constriction; □, 180°; △, 90°

bend needed between 8 and 25 mmHg. The material exhibited 'plug flow' in each tube.

Discussion

The evidence as to whether anorectal angulation is important in maintaining continence is conflicting. Although an obtuse angle is found in patients with idiopathic faecal incontinence[9], the success of the postanal repair operation[2,8], which was designed to recreate the acute angle without affecting anal pressure[3], does not correlate with the degree of anorectal angulation achieved[16–18]. Further doubt was cast on the role of angulation in creating a flap valve when it was observed radiologically that the anterior rectal wall did not make contact with the top of the anal canal during the Valsalva manoeuvre[12]. Despite this, it is recognized clinically that patients who have a divided sphincter and poor anal canal tone but a preserved puborectalis and anorectal angle can be remarkably continent, although unable to avert the call to stool.

The present study has shown that to retain liquid in excised bowel required a mucosal seal in which the pressure was greater than or equal to intrareservoir pressure, irrespective of angulation. For semisolids, however, the situation was different: angulation of the bowel improved retention of semisolids at all occlusion pressures between 0 and 50 mmHg.

Tests to determine the physical properties of faeces[15,19,20] have shown that they vary considerably in viscosity[15,20], hardness and consistency[19]. The semisolid gel suspension was chosen because it is a homogeneous substance whose physical properties (density and viscosity) are comparable to those reported for soft faeces[15]. On inspection, it had the appearance of soft, well-formed stool.

Glass tubes were used to examine the dynamics of flow of the semisolid material. Flow around a 90° bend without a constriction required extra pressure, while flow through a 50 per cent constriction required even greater pressure; thus both a bend and narrowing in a rigid tube introduced resistance to flow for the semisolid. Theoretical analysis of flow through bends is lacking[21]: bends can be thought of as an equivalent length L_{eq} of rigid tubing[22] which introduce an additional frictional force as if an extra length of tubing equal to L_{eq} was interposed. The value of L_{eq} for a 90° angled tube similar in diameter to the human anorectum is 180 cm[22]. L_{eq} for a flexible tube may be even greater than that for a rigid tube[23].

Although these *in vitro* models did not attempt to replicate the complexities of the dynamic pressure, volume and angulation changes in the anorectum, it has been demonstrated that to retain semisolid material resembling soft faeces in a tube it is not necessary to seal it. The requirement is that the resistance to flow be equal to or greater than the force tending to move it. Thus, by extrapolation, semisolid material in the rectum does not need a flap valve to keep it from moving into the anal canal. It would appear that angulation or constriction alone would provide sufficient resistance to prevent movement, even when the rectum is subjected to a minor degree of external pressure. With higher degrees of intra-abdominal or peristaltic pressure, both angulation and occlusion pressure require to be enhanced. The opposite effect, i.e. reduction of resistance to flow by the anorectal angle becoming more obtuse and opening of the anal sphincter, occurs during simulated defaecation as observed during proctography[11,24–26].

The mechanism for the control of fluid is different; liquids flow easily round bends and require a complete seal to contain them in a tube. For a sphincter to provide a liquid seal the intraluminal pressure must be equal to or greater than the pressure on the liquid. In one study[12], liquid barium filled the rectum and it was observed that the seal was maintained by contraction of the anal sphincter muscles alone. The data from the present study suggest that, if semisolid contrast had been used, there may have been no requirement for the sphincter muscles to respond so vigorously.

Continence to liquid stool is explicable in terms of a delicate balance of pressures. When that balance is disturbed, for example by diarrhoea distending the rectum with increasing intrarectal pressure, leakage will occur unless sphincter pressure can match rectal pressure. When damage to the sphincter prevents the creation of an effective pressure barrier, there will be incontinence to liquid but not necessarily solid stool. It is recognized that there is periodic relaxation of the internal sphincter muscle to allow sampling of rectal contents[27,28]. The preservation of angulation between the rectum and anal canal probably allows this to occur safely, retaining semisolids and solids within the rectal ampulla while gas and liquid flow into the upper anal canal.

These findings may also explain the lack of correlation between angle and success of the postanal repair operation[16–18]. In particular, the observation that a 50 per cent stenosis creates more resistance to flow than a 90° angulation suggests that an operation which produces a relative stenosis may also improve continence for formed motions. Therefore, either the creation of stenosis or the recreation of angle or both would be beneficial in preventing the flow of semisolids. A longer anal canal length and a relatively fixed perineum, which would achieve a fixed anorectal angulation, also appear important in the maintenance of continence[16].

In conclusion, these *in vitro* studies confirm that, for the retention of semisolid material, angulation enhances the resistance to flow for any given occlusion pressure, suggesting that angulation does provide a physiological benefit in continence. Angulation, however, provides no benefit in the retention of liquid.

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Total anorectal reconstruction results in complete anorectal sensory loss

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Six patients underwent objective measurement of anorectal sensory function following abdominoperineal excision of the rectum and total anorectal reconstruction. No patient perceived neorectal distension as a desire to defaecate or as a feeling of flatus. Anal mucosal sensation was preserved in two patients in whom some anal mucosa was retained. These sensory deficiencies may result in faecal retention and incontinence in patients undergoing reconstructive surgery. The loss of rectal sensation suggests that the prime sensors of rectal filling may lie within the rectum itself.

Total anorectal reconstruction (TAR) following abdominoperineal excision of the rectum and anal canal has been developed to avoid the need for an abdominal stoma. The focus of published reports has been the method of anal sphincter reconstruction. There have been no quantitative studies of anorectal sensory function following TAR.

The location and nature of the receptors responsible for the detection of rectal filling and identification of rectal contents are unknown. The pelvic floor[1], anal canal[2], rectal mucosa[3], and muscularis[4,5] have all been proposed as sensory organs. The preservation of the rectoanal inhibitory reflex following coloanal anastomosis has led to the widespread belief that the site of the primary receptors for rectal distension lie in the pelvic floor. All of the putative rectal sensors are removed or severely damaged in TAR.

Patients who have had TAR present a unique physiological model, in which all specialized sensors in the rectum and anal canal have been removed. Sensors in the pelvic floor remain in place, although the pelvic floor is inevitably damaged by the procedure. The aim of this study was to elucidate what 'anorectal' sensory function remains after TAR.

Patients and methods

Twelve patients have undergone TAR after excisional surgery for anorectal malignant disease at this hospital. Six patients (four men) of mean age 59 (range 47–73) years were available for study. Median length of follow-up after TAR was 24 (range 3–60) months. The technique of reconstruction was similar in all patients. A standard abdominoperineal anorectal excision[6] was performed. The pelvic floor was divided in all cases. Where tumour clearance was not compromised, levator tissue was retained. A small amount of distal anal mucosa was preserved in two patients. It was impossible to salvage more than 0·5 cm mucosal length or more than 50 per cent of the circumference in either case. Four patients underwent a straight colonic pull-through, with colon sutured to perineal skin. Two patients had a colonic J pouch[7,8] fashioned and sutured to the perineal skin at its apex. The procedure was always covered with a defunctioning stoma. An electrically stimulated gracilis neoanal sphincter[9,10] was constructed approximately 3 months later. The stoma was closed in four patients, when the gracilis neosphincter had undergone fibre-type transformation from a fast (type 2) to a slow (type 1) phenotype[11]. One patient elected to keep the colostomy and another died from a myocardial infarct before the stoma was closed. Patients were tested for 'rectal' and 'anal' sensation.

Rectal sensory testing

A balloon distension technique was employed. The patient was placed in the left lateral position. A digital rectal examination was performed to ensure the colon proximal to the perineum was empty. A party balloon, mounted on a Foley catheter, was then introduced into the neorectum with the distal end lying 3 cm proximal to the gracilis neosphincter.

The balloon was inflated with water at 37°C at a rate of 80 ml per min using a constant rate infusion pump (Watson Marlow, Berkshire, UK). The nature of the first sensation and the volume at which it was perceived were recorded. The procedure was repeated twice.

Neoanal sensation

Neoanal sensation was assessed using a mucosal electrosensitivity technique[12]. A mucosal electrosensitivity probe was constructed from two urethral ring electrodes (Dantec, Bristol, UK) mounted on a Foley catheter. The device was placed in the neoanus with the distal ring electrode situated 0·5, 1·0 and 1·5 cm from the mucocutaneous junction. An alternating current (5-Hz 200-ms pulse width) (BESA, Bristol, UK) was passed between the electrodes and increased until the patient reported a stinging or tingling sensation or maximum of 25 mA was reached.

Results

Neorectal sensation

The results are expressed as the mean of three threshold sensory neorectal volumes recorded for each patient (*Table 1*). The first sensation in all patients was pain. It was considered that further balloon distension could not be justified.

No patient reported a feeling analogous to the presence of flatus or faeces in the rectum. No control group has been included: comparison between patients undergoing TAR and normals would be meaningless since the painful sensory threshold observed in the present patients is not comparable to normal rectal sensation.

None of the four patients with a functioning reconstruction has reported any subjective sensation of defaecatory desire. All four have adopted strategies based on attempting to establish a predictable pattern of colonic motility, allowing them to remain near a lavatory when defaecation is likely to occur.

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Table 1 Threshold neorectal sensory volume and perceived sensation

Patient no.	Mean sensory threshold volume (ml)	Perceived sensation
1	72	Abdominal pain
2	305	Abdominal pain
3	114	Perineal pain
4	26	Abdominal pain
5	107	Perineal pain
6	135	Perineal pain

Neoanal sensation

An electrical sensory threshold of 13·2 and 14·3 mA was identified at the 0·5-cm position in patients in whom some anal mucosa had been preserved. Neither of these patients perceived the stimulus 1·0 or 1·5 cm from the mucocutaneous junction. None of the other four patients perceived the stimulus at any site.

Discussion

Chittenden[13] was probably the first to attempt TAR when he wrapped slips of gluteus maximus around the mucocutaneous junction of a patient who had undergone a previous Kraske procedure for rectal carcinoma. A number of reports since then have focused on the construction of smooth muscle[14–16] or skeletal muscle[9,17–22] neosphincters. Little attention has been paid to the sensory consequences of TAR.

The balloon distension test stimulates the rectum by centrifugal expansion and, since the rectum normally fills from above, cannot be considered a truly physiological test of rectal sensation. The presence of a tube in the anal canal is an additional confounding variable. It is the only method that attempts to mimic normal rectal filling and is the most commonly employed test of rectal sensory function. Progressive distension in normal subjects results in a threshold sensory volume, usually interpreted as a feeling of flatus, a defaecatory desire volume and maximum tolerated volume. The technique has been shown to be repeatable[23,24], although measured values depend on the size of the balloon and rate of filling[24]. Water at 37°C was used in the present study to minimize the possibility of thermal sensation confounding the measurement. The results demonstrate a complete absence of objective and subjective rectal sensation following TAR, and are at variance with subjective data reported by some authors.

Cavina *et al.*[19] and Simonsen and colleagues[18] performed total reconstruction by a straight coloperineal anastomosis with a gracilis neosphincter. Cavina *et al.*[19] found that ten of 25 patients assessed were able to perceive solid stool in the neorectum. Twelve patients were able to differentiate gas, liquid and solid, and only two were completely devoid of any anorectal sensation. Simonsen and co-workers[18] found that most patients were able to sense neorectal filling, although only five of 22 had a feeling 'similar to normal'. Both groups found that patients in whom anorectal sensation was absent had the least satisfactory result.

The absence of objective data in the study of Cavina *et al.*[19] makes it difficult to draw firm conclusions about the nature of the sensation in that series. Patients may learn to interpret abdominal pain or distension as a signal for the need to defaecate. Direct questioning of patients about rectal sensation introduces observer bias. A problematic finding is maintenance of the ability to detect flatus in some patients[19]. In normal subjects the anal canal probably detects flatus through the sampling reflex. In reconstructed patients the specialized anal mucosa is lost and the pelvic floor is unlikely to be responsible for the perception of flatus.

Mucosal electrosensitivity is an established correlate of anal sensory function[12,25]. It has been shown to be a highly repeatable measurement in faecal incontinence[26]. The present data demonstrate that salvage of anal mucosa during TAR does result in the preservation of some anal sensation and that excision of the specialized anal mucosa causes loss of sensation.

It is possible that the pelvic floor might provide some form of rectal sensation. In TAR the pelvic floor is inevitably divided and damaged. However, if it were the sensor for rectal distension, some 'rectal' sensation might have been likely in the present patients. The complete absence of any such sensation suggests that the prime sensor for rectal filling lies within the rectum itself.

The sensation of rectal filling is mediated by fibres entering the central nervous system through the second, third and fourth sacral nerves[27]. Cortical evoked potentials have been recorded after both electrical[28,29] and mechanical[30] stimulation of the rectum. Kamm and Lennard-Jones[31] demonstrated the presence of sensory nerve fibres in the rectum with a mucosal electrosensitivity technique. Goligher and Hughes[32] found that the rectum was least sensitive to distension proximally, becoming progressively more sensitive as the anal canal was approached. Broens *et al.*[33] studied rectal sensation in normal volunteers, in the sitting position, by distending the rectum with a balloon containing gas, water or mercury. Sensation was related only to the size of the balloon, not to balloon mass, suggesting that stretching of the pelvic floor is not an important mediator of rectal sensation. Studies of rectal sensation following coloanal, ileal pouch–anal and colonic pouch–anal anastomosis tend to support the hypothesis that rectal sensation is diminished by the loss of the rectum itself[32,34–36].

This study has shown a complete loss of anorectal sensation following anorectal excision and TAR. This sensory deficit resulted in the inability of patients to perceive imminent defaecation. Patients with TAR have been forced to adapt their lifestyle around the anticipated behaviour of the colon. This imposes marked limitations on an individual's freedom of movement.

The loss of all anorectal sensation after TAR provides further evidence that the rectum is supplied by a specialized sensory innervation. The theory that rectal filling is perceived primarily via the pelvic floor no longer appears tenable.

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Anastomotic leakage and functional outcome after anterior resection of the rectum

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Nineteen patients with symptomatic anastomotic leakage after anterior resection were compared with 19 without leakage. The two groups were closely matched according to age, sex, height of anastomosis and follow-up. No patient had any sign of anastomotic stricture or neoplastic recurrence at the time of the study. After a median of 30 (range 12–87) months there was no difference in sphincter function as measured by manometry. 'Neorectal' volume at distension pressures of 40 and 50 cmH$_2$O and compliance at sensation of filling, urge to defaecate and maximum tolerated volume were significantly reduced in patients with leakage. This reduction in neorectal reservoir function was reflected in impaired anorectal function, measured by a combination of: (1) frequency of bowel movements; (2) degree of urgency; (3) incontinence score; and (4) degree of impaired evacuation. Long-term functional outcome may be impaired by anastomotic leakage.

Anastomotic leakage is the most significant complication after anterior resection of the rectum and is the major cause of postoperative mortality and morbidity[1–3]. The reported incidence of symptomatic leakage, regardless of the use of stapler or protecting stoma, is approximately 10 per cent[3–6], and was higher in earlier series[1]. As a result of pelvic sepsis, fibrosis may develop with subsequent narrowing of the distal bowel or stricture formation, but little is known about the long-term effect of leakage on bowel function. The aim of this study was to investigate whether anastomotic leakage, even after healing without anastomotic stricture, is associated with changes in the physiology and clinical function of the distal bowel.

Patients and methods

Patients

In the 7 years to July 1991, 283 patients with rectal carcinoma underwent anterior resection; symptomatic anastomotic leakage occurred in 34 (12 per cent) from evidence of abscess on computed tomography or ultrasonography, discharge of a pelvic collection either *per anum* or via a fistula, or the need for laparotomy or a transanal drainage procedure. Nineteen successfully treated patients with restored bowel continuity for at least 1 year and with no evidence of stricture formation or recurrent malignant disease form the basis of this report. A further 19 patients without anastomotic leakage were identified who were closely matched in terms of age, sex, height of anastomosis above the anal verge and length of follow-up (*Table 1*). One patient in each group received preoperative X-ray treatment (25 Gy). The anastomosis was sutured in one patient in each group, double stapled in three (no leakage) and eight (leakage group), and in the remainder stapled with a distal purse-string suture.

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Table 1 Characteristics of the 38 patients in the study

	Leakage ($n = 19$)	Controls ($n = 19$)
Sex ratio (M:F)	8:11	8:11
Median (range) age (years)	65 (52–83)	69 (55–86)
Median (range) follow-up (months)	28 (12–79)	32 (12–87)
Median (range) anastomotic height above anal verge (cm)	6 (4–11)	7 (4–12)
Part of colon used for reconstruction (sigmoid:descending)	13:6	15:4
Protective stoma at the primary operation	8	5

Management of leakage is shown in *Table 2*. One patient without leakage and five in the leakage group were dilated from below because of a benign anastomotic stricture precluding the passage of a rigid rectoscope 18 mm in diameter.

All patients participating in the study answered a questionnaire regarding anorectal function and were examined by means of anorectal manometry, manovolumetry and rigid rectoscopy.

Evaluation of anorectal function

A questionnaire with the following items was used:

1 Frequency of bowel movements (24 h), calculated as the average noted on a 7-day diary card.
2 Degree of urgency: 0, 1, 2, 3 (ability to defer defaecation for 30 min: always, often, sometimes, never).
3 Composite score of grade and frequency of faecal incontinence (modified from Miller *et al.*[7]) (*Table 3*).

Table 2 Management of anastomotic leakage in 19 patients

	No stoma ($n = 11$)	Stoma ($n = 8$)
Urgent laparotomy	5	0
Transanal drainage	3	5
Spontaneous drainage *per anum*	3	1
Conservative treatment (antibiotics only)	0	2

Table 3 Incontinence score system*

Frequency	Flatus	Liquids	Solids
Never	0	0	0
Less than once a week	1	4	5
More than once a week, but less than daily	2	5	7
Daily	3	6	9

*Maximum score 18; the score is determined by adding points from the grid, which takes into account the grade and frequency of incontinence of bowel contents

4 Degree of impaired evacuation: 0, 1, 2, 3 (ability to evacuate the bowel in less than 15 min: always, often, sometimes, never).

The questionnaire was answered by patients at home and was administered separately by a nurse who was blinded to the group for each patient.

Anorectal manometry and manovolumetry

A microtransducer catheter was used with the station pull-through technique to assess sphincter function. Details and results of the manometry method have been published previously[8].

The manovolumetry method, described in detail elsewhere[9,10], was used to assess reservoir function of the distal bowel, the 'neorectum'. Volume changes in the distal bowel were recorded as a response to isobaric distension at defined distension pressures. A pressure–volume curve was generated by a series of distensions with 10-$\mathrm{cmH_2O}$ increments. Compliance (ml per $\mathrm{cmH_2O}$) at the sensory threshold for appreciation of filling, urge to defaecate and maximum tolerated volume was calculated.

Statistical analysis

The Wilcoxon rank sum test was used unless otherwise stated. The values are presented as median (interquartile range) unless otherwise stated. A two-sided level of 0·05 was accepted as significant.

Four variables were considered on *a priori* grounds to be the most sensitive indicators of the anorectal function. An overall test of the difference in bowel function between the groups was based on a combination of these four variables. The results for each of the four variables were ranked in all patients from most to least favourable. The mean of the four ranks obtained for each patient was used as a combined indicator of how anorectal function was rated. The Wilcoxon rank sum test was used to compare groups. The general method of combining data by averaging rank numbers has been discussed by O'Brien[11].

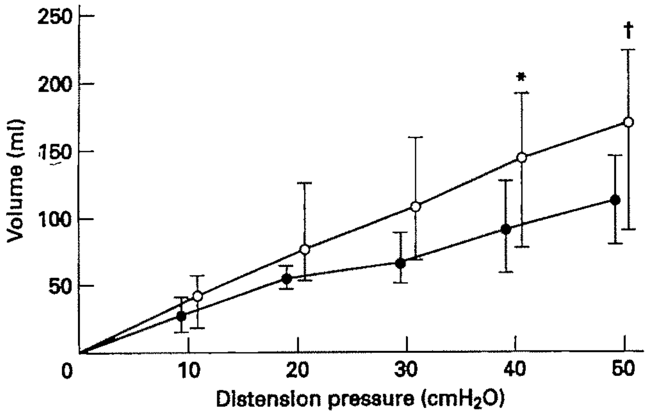

Fig. 1 'Neorectal' volume at defined distension pressures obtained by manovolumetry. ○, Controls $(n = 19)$; ●, patients with anastomotic leakage $(n = 19)$. Values are median (interquartile range). $^*P = 0·04$, $^\dagger P < 0·05$ (leakage *versus* control, Wilcoxon rank sum test)

Results

The median follow-up was 30 (range 12–87) months. There was no difference in sphincter function between the groups but the neorectal volume at distension pressures of 40 and 50 $\mathrm{cmH_2O}$ was significantly lower in patients with leakage (*Fig. 1*). The compliance values at sensation of

Table 5 Anorectal function variables

	Leakage $(n = 19)$	Controls $(n = 19)$	P†
Frequency of bowel movements per 24 h	4 (3·5–5·0)	2 (1·5–5·0)	0·02
Degree of urgency (0–3)*	1 (0–2)	0 (0–2)	0·06
Composite score of incontinence (0–18)*	5 (2–7)	2 (0–7)	0·14
Degree of impaired evacuation (0–3)*	0 (0–1)	0 (0–1)	0·97

Values are median (interquartile range). *0 = no urgency, incontinence or evacuation difficulty. †Wilcoxon rank sum test

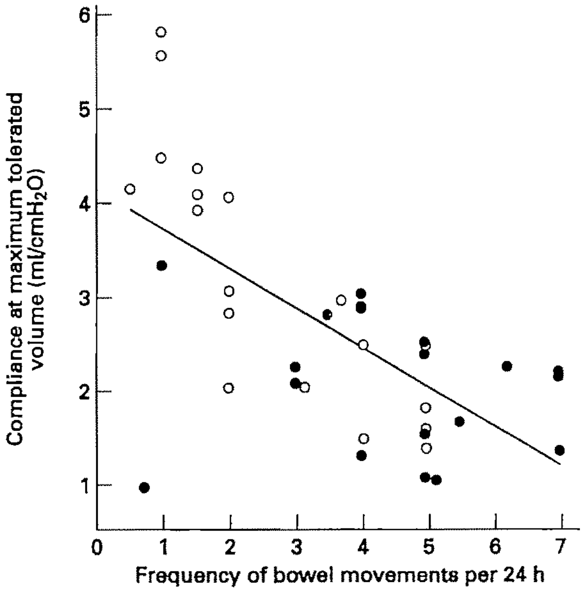

Fig. 2 Correlation between compliance of the 'neorectum' at maximum tolerated volume and frequency of bowel movements per 24 h. ○, Controls; ●, patients with anastomotic leakage. $r_S = -0·62$, $P < 0·0001$

Table 4 'Neorectal' volume and compliance

	Leakage $(n = 19)$	Controls $(n = 19)$	P*
Volume at distension pressure of 40 $\mathrm{cmH_2O}$ (ml)	90 (58–133)	144 (75–195)	0·04
Compliance at sensation of filling (ml/$\mathrm{cmH_2O}$)	2·1 (1·4–3·2)	4·0 (2·6–6·3)	0·02
Compliance at urge (ml/$\mathrm{cmH_2O}$)	2·5 (1·3–3·0)	3·5 (2·1–6·0)	0·04
Compliance at maximum tolerated volume (ml/$\mathrm{cmH_2O}$)	2·2 (1·5–2·8)	3·0 (1·8–4·2)	0·04

Values are median (interquartile range). *Wilcoxon rank sum test filling, urge to defaecate and maximum tolerated volume were significantly lower in the leakage group (*Table 4*). The median rank score of the combination of frequency, urgency, incontinence and impaired evacuation was significantly higher (23·6 *versus* 16·5) for the leakage group ($P = 0{\cdot}03$), indicating impaired function. When the four variables were compared separately, frequency of bowel movements was significantly higher in patients with leakage but the increase in degree of urgency and incontinence score was not statistically significant (*Table 5*). The ability to evacuate was similar in both groups. There was a significant negative correlation between frequency of bowel movements and compliance at maximum tolerated volume (*Fig. 2*).

Discussion

Parks and Percy[12] emphasized the importance of avoiding pelvic sepsis and its attendant risk of fibrosis resulting in poor anorectal function. To investigate the role of symptomatic anastomotic leakage in functional outcome a matched-pair design was chosen to reduce bias from confounding factors. It was not possible, however, to match according to part of colon used for the anastomosis or the use of a protecting stoma. In the group with leakage the descending colon was used for the anastomosis in six patients, compared with four in the controls. It may be of some relevance as the advantage of using the descending colon has recently been reported[13]. A protecting stoma was used in eight and five patients respectively. These differences between the groups were not statistically significant. Absence of anastomotic stricture at the time of investigation was verified in all patients.

The sphincters and the distal intestinal reservoir are important factors in anorectal function. The sphincters seemed to function equally in the two groups but the decreased volumes and compliance values in patients with anastomotic leakage imply that the reservoir function of the distal bowel was impaired, reflected by the impaired function measured by the combination of four symptom-related variables of anorectal function. The negative correlation between frequency and compliance was an indicator of this relationship.

Anorectal function is a complex entity which cannot be described satisfactorily by one single variable such as frequency of bowel movements. The average rank test used was an attempt to avoid the dependence on cut-off levels that is inevitable when building functional score systems.

The manovolumetry method has been used to compare different ileal pouch designs[14], but the interpretation of compliance values is debatable. To describe reservoir function, volume measurements at defined distension pressures and calculated compliance values at points related to the sensory function were used, as proposed by others[15].

In addition to the immediate risk for the patient, anastomotic leakage may increase the risk of neoplastic recurrence[16]. These results imply that anastomotic leakage also affects the long-term functional outcome.

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Ischaemic nature of anal fissure

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Microvascular perfusion of the anoderm was assessed by laser Doppler flowmetry in 27 patients with anal fissure. Anal pressure was recorded simultaneously. Both measurements were repeated 6 weeks after lateral internal sphincterotomy and compared with those obtained from 27 controls. Mean(s.d.) maximum anal resting pressure was significantly higher in those with a fissure than in controls (121·07(24·48) *versus* 68·78(16·97) mmHg, $P<0{\cdot}001$). Anodermal blood flow at the fissure site was significantly lower than at the posterior commissure of the controls (0·46(0·20) *versus* 0·76(0·28) V, $P<0{\cdot}001$). The fissure healed in 24 patients within 6 weeks of sphincterotomy. In these patients a significant pressure decrease was noted (35 per cent) which was accompanied by a consistent rise in blood flow (65 per cent) at the original fissure site. The increased internal sphincter tone in patients with a fissure reduces anodermal blood flow at the posterior midline. Reduction of anal pressure by sphincterotomy improves anodermal blood flow at the posterior midline, resulting in fissure healing. These findings provide evidence for the ischaemic nature of anal fissure.

Despite attempts to elucidate the pathogenesis of anal fissure, the cause of this painful condition is still unknown. None of the theories provides an explanation for its poor healing rate and predilection for the posterior midline location. Furthermore, they cannot explain other characteristic features of anal fissures, such as severe pain, lack of granulation tissue at the fissure site, and the absence of lateral epidermal regrowth.

It has been proposed that increased sphincter pressure may cause ischaemia of the anal lining[1]. This was supported by the results of an angiographic post-mortem study which revealed that the small branches of both inferior rectal arteries passing though the internal anal sphincter have no, or only minimal, contact at the posterior commissure in 85 per cent of cases[2].

In a previous study[3], aimed at evaluating the relationship between anal pressure and anodermal blood flow, the blood supply of the anoderm at the posterior midline was found to be significantly lower than at the other sides of the anal canal. Furthermore, a significant relationship between anal pressure and anodermal blood flow was demonstrated at the posterior midline. The higher the pressure, the lower the blood flow[3]. In view of these findings a prospective study of patients with chronic anal fissure was started. Before and 6 weeks after lateral internal sphincterotomy both anorectal manometry and laser Doppler flowmetry of the anoderm were performed to provide more evidence for the ischaemic nature of anal fissure.

Patients and methods

Between November 1992 and April 1994, 27 consecutive patients with chronic anal fissure were studied. This group consisted of 19 women and eight men with a median age of 35 (range 23–64) years. All patients had an anal fissure for more than 3 months. These fissures showed features of chronicity, such as exposure of the internal anal sphincter, induration of the fissure edges, development of a large sentinel pile and hypertrophied anal papilla. All fissures were located at the posterior midline. Lateral internal sphincterotomy was performed on an outpatient basis under local anaesthesia. Before and 6 weeks after this procedure each patient had anorectal manometry and laser Doppler flowmetry Both measurements were also performed in 27 normal volunteers. This group comprised 19 women and eight men. Their median age was 39 (range 19–88) years. In all participants anodermal blood flow was assessed at the posterior midline. In a subgroup consisting of nine patients and 14 controls microvascular perfusion of the anoderm was also assessed at both lateral sides of the anal canal as well as in the midline anteriorly.

Laser Doppler flowmetry

Microvascular perfusion of the anoderm was assessed by laser Doppler flowmetry with a Periflux PF2B laser Doppler flowmeter (Perimed, Stockholm, Sweden) This instrument contains a low-power helium–neon laser, that generates a narrow beam of monochromatic light. For the purpose of this study a special angled probe (PF 306, Perimed) was developed with an external diameter of 2·3 mm. Three optical fibres were incorporated in this probe; one for transmission of laser light (wavelength 632·8 nm) and two for transport of reflected light. Before each measurement the room temperature was adjusted to 22°C. All recordings were performed by one investigator (W.R.S.). The measurements were obtained without bowel preparation and with the participant in the left lateral position with hips and knees flexed at 90°. After introduction into the anal canal the probe head was applied to the fissure site, in some patients it was also applied to the anoderm of the anterior commissure as well as to that of each lateral side of the anal canal. Blood flow at each location was measured for a period of 4 min. Pressure to the underlying anoderm was avoided to prevent occlusion of the microvessels. During each measurement the probe was held by hand. The flux is expressed in volts.

Anorectal manometry

Anal pressures were measured by a micro-tip pressure transducer (Millar Instruments, Houston, Texas, USA) with an external diameter of 1·7 mm. In each participant the catheter was introduced into the rectum until rectal pressure was recorded. The probe was then pulled out manually. This manoeuvre was repeated three times. Mean value of maximum anal resting pressure was determined for each participant

Statistical analysis

The Wilcoxon rank sum test was used to compare maximum resting anal pressure with anodermal blood flow in patients with anal fissure and controls. Measurements before and after

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Table 1 Maximal anal resting pressure and anodermal blood flow, expressed as flux, in patients with chronic anal fissure before and after lateral internal sphincterotomy and controls

	Maximal anal resting pressure (mmHg)	Anodermal blood flow	
		Location	Flux (V)
Controls ($n = 27$)	68·78(16·97)	Posterior ($n = 27$)	0·76(0·28)
		Anterior ($n = 14$)	1·31(0·65)
		Left ($n = 14$)	1·48(0·93)
		Right ($n = 14$)	1·30(0·53)
Patients with chronic anal fissure Before lateral internal sphincterotomy ($n = 27$)	121·07(24·48)*	Posterior ($n = 27$)	0·46(0·20)*
		Anterior ($n = 9$)	0·85(0·81)‡
		Left ($n = 9$)	1·78(0·73)
		Right ($n = 9$)	1·61(1·07)
After lateral internal sphincterotomy ($n = 26$)	79·46(23·17)†	Posterior ($n = 26$)	0·77(0·15)†
		Anterior ($n = 9$)	1·04(0·47)
		Left ($n = 9$)	1·72(0·76)
		Right ($n = 9$)	1·32(0·72)

Values are mean(s.d.). *$P < 0·001$ *versus* controls (Wilcoxon test); †$P < 0·001$ *versus* patients with chronic anal fissure before sphincterotomy (paired *t* test); ‡$P < 0·05$ *versus* controls (Wilcoxon test)

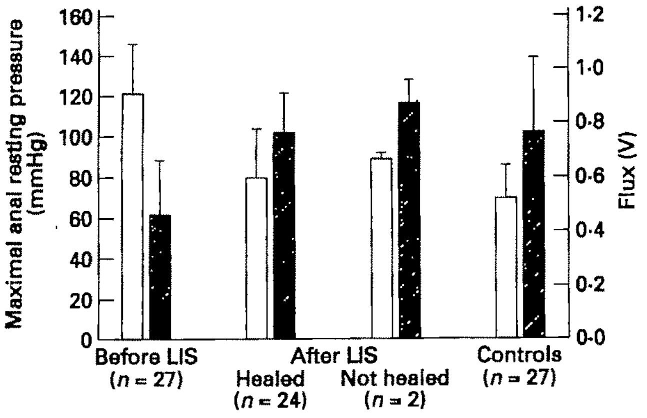

Fig. 1 Maximum anal resting pressure (☐) and anodermal blood flow (▨) expressed as flux in controls and patients with fissures before and after lateral internal sphincterotomy (LIS). Values are mean(s.d.)

sphincterotomy were evaluated by paired *t* tests. $P < 0·05$ was considered significant. Results are given as mean(s.d.).

Results

Maximum resting anal pressure in patients with chronic anal fissure was significantly higher than that in controls (*Table 1*). Blood flow at the fissure site was significantly lower than at the posterior commissure of the anoderm in the controls. On the lateral sides of the anal canal no difference was found between perfusion in patients with anal fissure and controls. By contrast, anodermal blood flow, measured at the anterior midline, was significantly lower in patients with a fissure.

The fissure had healed in 24 patients 6 weeks after lateral internal sphincterotomy. One patient was lost to follow-up. Symptomatic relief was not obtained by two patients in whom the fissure persisted. Patients with healed fissures had a significant pressure decrease (35 per cent), which was associated with a consistent increase (65 per cent) in anodermal blood flow at the original fissure site. Both maximal anal resting pressure and anodermal blood flow regained normal values after successful sphincterotomy (*Fig. 1*). Similar changes were found in two patients with a persistent fissure. Perfusion of the anoderm of each lateral side of the anal canal showed no significant alteration after sphincterotomy. A considerable increase in blood flow at the anterior midline was found after the sphincter-cutting procedure; however, this was not statistically significant, probably because of the small number of patients.

Discussion

High resting anal pressure because of increased activity of the internal anal sphincter is found in almost all patients with chronic anal fissure[1,3–9]. It is still generally accepted that the increased activity is a reaction of the internal anal sphincter to pain. High anal pressure is considered the consequence rather than the cause of chronic anal fissure. It has been postulated, however, that increased anal pressure precedes anal fissure[1]. There is evidence that psychological stress produces a sustained tonic rise in anal canal pressure, reflecting increased tone in the internal anal sphincter[10]. Rats submitted to stress develop molecular changes in β_1-adrenergic receptors[11]. The internal anal sphincter of patients with chronic anal fissure shows increased sensitivity to β_2-agonists[11]. Stress might be a factor in the pathogenesis of anal fissure.

In a post-mortem angiographic study the small branches of the inferior rectal artery were shown to pass through the intermuscular septa of the internal anal sphincter in a direction perpendicular to the muscle fibres. This study also revealed that the branches of both arteries have either no or minimal contact at the posterior midline[2]. These findings suggest that the posterior commissure is less well perfused than other segments of the anoderm. The intraluminal arteriolar pressure is approximately 85 mmHg. Normal anal canal resting pressure is within this range. Patients with anal fissure have significantly higher pressure, exceeding the intraluminal pressure of arterioles. Increased activity of the internal anal sphincter may further decrease the anodermal blood supply, especially at the posterior midline, by compression of arterioles arising from the inferior rectal arteries. The authors have previously reported that the blood supply of the anoderm at the posterior midline in healthy volunteers is significantly lower than at other sides of the anal canal[3], and could demonstrate a significant relationship between anal pressure and anodermal perfusion at the posterior commissure.

The present study suggests that the tonic rise in anal pressure contributes to impaired perfusion at the fissure site and, to a lesser extent, at the anterior midline, where one of ten fissures is located.

Six weeks after successful lateral internal sphincterotomy a significant pressure decrease was found, together with a consistent increase in anodermal blood flow at the original fissure site. Similar alterations were also found in two patients with a persistent fissure, which is difficult to interpret. Delayed fissure healing might be one possible explanation, persistent ischaemia may be another, although normal values for anodermal blood flow and anal pressure were regained in each patient. However, both patients may have had lower anal pressures preceding the development of their fissure than after sphincterotomy. Therefore 'normal' values after operation may be considered abnormal compared with pre-existing values. Nevertheless, reduction in internal sphincter tone reflected by the decrease in anal resting pressure allows sufficient resumption of anodermal blood supply for fissure healing in most patients. In the authors' opinion traumatic laceration of the anoderm is the major initiating factor. In individuals with normal anal pressures such a laceration will heal spontaneously. In patients with a pre-existing rise in internal sphincter tone (possibly caused by stress), traumatic lesions of the anoderm heal poorly. This failure to heal is mainly caused by impaired perfusion of the anoderm, especially at the midline posteriorly, which finally results in ischaemic ulceration. The ischaemic nature of chronic anal fissure explains the characteristic features of this painful condition.

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Surgical workshop

New technique for subcuticular suture in lengthy wounds

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Subcuticular sutures used for cosmetic skin approximation usually produce a satisfactory scar. Non-absorbable monofilament sutures further increase the advantages of subcuticular closure[1,2], but in lengthy wounds it is difficult to use fine material such as 3/0 or 4/0, as it may break on withdrawal.

Several methods have been employed to secure the loose ends of running subcuticular stitches. Beads and bulky knots may produce an unsightly scar at the ends of the suture line. For several years the author has used a technique for non-absorbable subcuticular sutures that allows sound wound approximation, minimal scarring and can be applied to lengthy wounds.

Surgical technique

Subcuticular suturing is started by inserting the stitch 5 mm proximal to the end of the wound (*Fig. 1*). The free end (A) is held in the left hand and a loop is formed around the index finger and thumb of the right hand. Through this loop a bight of the thread towards the skin (B) is grasped between the right index finger and thumb, and drawn through the loop, which is then tightened. This forms a slip knot that slides until it impinges on the skin surface. Another two to three hitches may be made between the loop of the knot and the free end to create a bulkier knot. As subsequent subcuticular stitches are inserted, the needle can be brought out and back through the same hole at intervals of 5–6 cm. The resulting loop can be formed into a slip knot which is adjusted on to the skin surface before being tightened. Two to three further hitches can be done in turn, to reinforce the knot, if desired.

If the suture breaks, or is too short, another suture can be tied around the emerging end with a sliding knot comprising two half hitches[3]. This is then drawn down to the skin surface to secure the end and tightened. Suturing can now be continued.

When closure is complete, the needle is pushed through to emerge 5 mm beyond the end before forming the final slip knot to secure the suture (*Fig. 2*).

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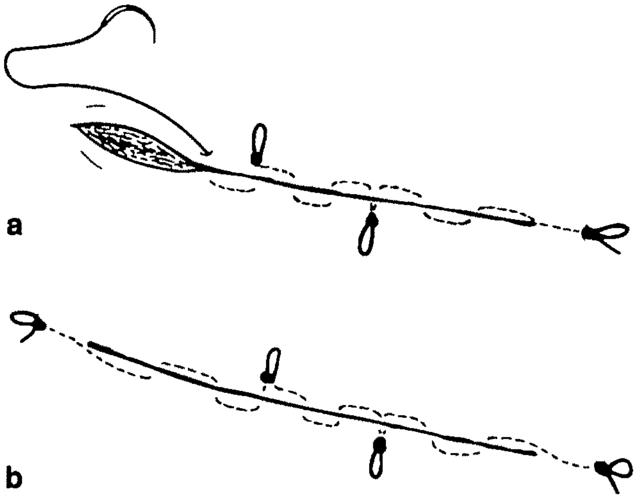

Fig. 2 a Technique of subcuticular suture with side knots in a lengthy wound; b subcuticular suture is completed

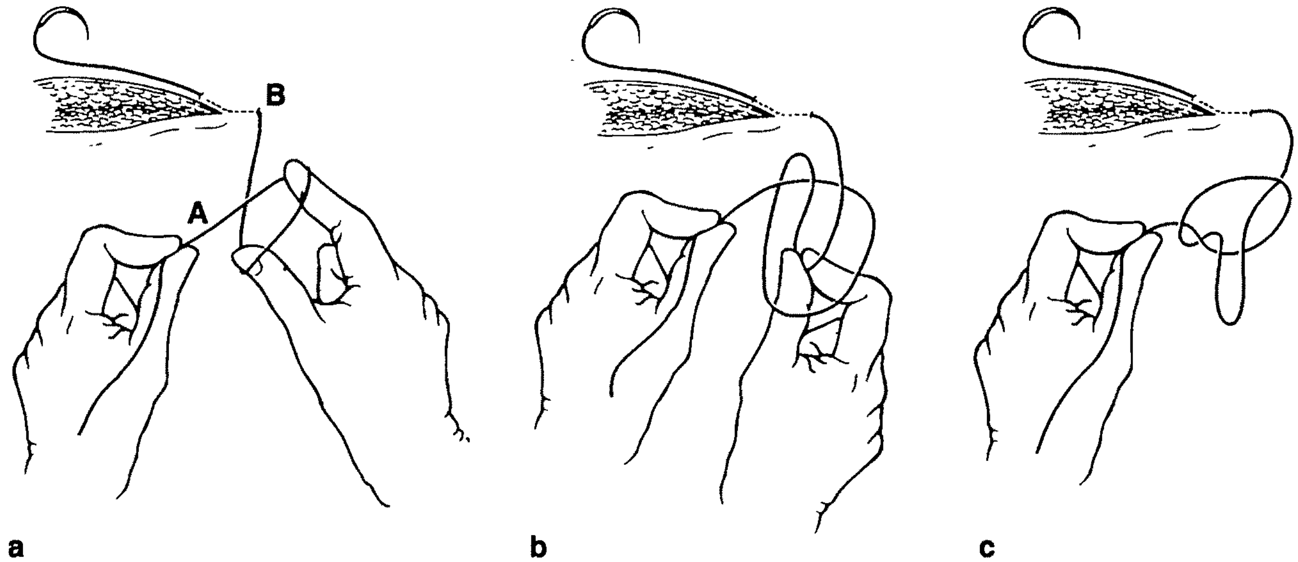

Fig. 1 a–c Steps to start the knot for subcuticular suture

When the suture is to be removed, the segment between contiguous loops can be pulled out individually after cutting the loops.

Discussion

The technique is simple, economical of suture material and results in minimal or no scarring. It can be applied to any wound and is particularly valuable when using fine material in lengthy wounds. The suture can be removed piecemeal.

Acknowledgements

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Thoracic and thoracoabdominal aortic aneurysm and dissection: an investigation based on autopsy

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The city of Malmö (population approximately 230 000) has a fairly stable urban population and a high autopsy rate (83 per cent of all deaths). Autopsy records for the period from 1958 to 1985 were scrutinized and three groups of patients were defined: those with asymptomatic thoracic aortic aneurysm (TAA), those with rupture of the thoracic aorta, and those with dissection. The findings were used to calculate prevalence and incidence according to age and sex. Asymptomatic TAA was found in 205 patients (109 men). There was a predominance of men in higher age groups and about 5 per cent of the lesions were thoracoabdominal. Rupture of the thoracic aorta was the cause of death in 63 patients; no age difference between the sexes was observed. Death as a result of dissection occurred in 216 patients, women dying on average 7 years later than men. The incidence of rupture was 0·9 per 100 000 for men and 1·0 per 100 000 for women; the incidence of dissection was 3·2 per 100 000 for both sexes. Prevalence and incidence of fatal complications of TAA are low; this may influence decisions about where these patients should be treated.

After the first successful operation for abdominal aortic aneurysm (AAA) by Dubost *et al.*[1] in 1952, the number of aneurysm operations increased greatly. Indeed, there appears to be a continuing increase even at the present time in both elective and emergency operations[2]. This is because of several factors: better diagnostic methods and results after surgery, more elderly people in the population, and an increasing prevalence of AAA itself, i.e. after correction for variation in age of the population[3–6]. Although AAA occurs at a site of arteriosclerotic degeneration[7], in recent years other factors have also been implicated in the aetiology and pathogenesis of aneurysms; these point to important genetic associations[8–11].

For thoracic aortic aneurysm (TAA), epidemiology and pathogenesis are slightly different. As syphilis and tuberculosis are aetiological factors in the development of some TAAs, the decreased frequency of such infections might have reduced the prevalence of TAA; whether or not this is the case is not known. What is certain is that thoracoabdominal aneurysm involving the large visceral vessels is a major challenge in vascular surgery. Nevertheless, as a result of technical innovations[12], the surgical treatment of this type of aneurysm has been established in several institutions. At centres where thoracoabdominal aneurysm surgery is carried out, a high demand is placed on hospital resources. Further knowledge of the prevalence of TAA is desirable for proper planning of health care delivery.

The aim of this study was to estimate the prevalence of TAA by determining the occurrence of autopsy-verified TAA in the period from 1958 to 1985, and to calculate the incidence of non-traumatic ruptured TAA and dissection of the thoracic aorta. Time trends in the prevalence of TAA were also studied.

Patients and methods

The autopsy registers of the departments of pathology and forensic medicine covering the interval from 1958 to 1985 were examined. Only patients who were resident in the city of Malmö at the time of death were included in the study. The system of registration at the department of pathology is of high validity[3]; the corresponding autopsy records were examined to confirm the register data. Throughout the period all autopsies and recording of findings were performed in a standardized way. In addition, during the entire period the department of pathology had a special interest in vascular diseases and all autopsies were supervised by senior pathologists. In cases of aneurysm or dissection, information on the location, size and whether rupture had occurred was collected, as well as histopathology. Data on the presence of aneurysm were based on the description and classification of the pathologist conducting the autopsy. Aneurysm rupture caused by trauma was clearly described by the pathologist and was not included. Patients were classified into three groups: (1) asymptomatic TAA; (2) rupture of the thoracic aorta; and (3) dissection of the thoracic aorta. An asymptomatic TAA was defined as an aneurysm detected at autopsy which did not directly cause death. Rupture was defined as blood penetration of all layers of the aortic wall, gaining access to some extra-aortic part of the thoracic cavity. Dissection was defined as the presence of blood between layers of the aortic wall, and dissection eventually causing penetration of all layers of the wall, with entry of blood into the thorax, was considered dissection rather than rupture.

The patients were divided into 12 age groups: 0–39, 40–89 (in multiples of 5 years), and 90 years and over. Men and women were considered separately. The annual age- and sex-specific occurrence of asymptomatic TAA was calculated as the ratio between the number of aneurysms and the number of autopsies performed in that age group. The age-standardized occurrence of asymptomatic TAA for each year was calculated by using the number of autopsies performed in each age group in 1970 as a standard. The percentage of aneurysms in each of the 12 age groups each year was multiplied by the number of autopsies in the corresponding age groups in 1970. The results for the 12 age groups were added and then divided by the total number of autopsies in 1970. Age standardization was performed separately for men and women.

Population statistics for the period under study were obtained from Malmo City Office (department of planning and statistics). During the period from 1958 to 1985 the population of Malmö varied between 221 664 (sex ratio (M:F) 48·1.51·9) to 229 936 (sex ratio (M:F) 47·5:52·5), with a peak population in 1970 of 264 563 inhabitants. During the period from 1958 to 1985, 70 368 citizens of Malmo died. Of these, 63 per cent underwent autopsy at the department of pathology and 20 per cent at the

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department of forensic medicine. The remaining 17 per cent did not undergo post-mortem examination. The frequency of autopsies varied over time, but remained consistently high (*Fig. 1*). Approximately 1 per cent of the patients residing in Malmö underwent autopsy at the department of pathology in the nearby city of Lund after dying at the department of neurosurgery. These patients were excluded from this study.

Analysis of difference in age was performed using the Mann–Whitney *U* test and analysis of group proportions using the χ^2 test. Statistics on prevalence and incidence changes over time were performed by linear regression analysis. Tests were two-tailed and $P < 0.05$ was considered significant.

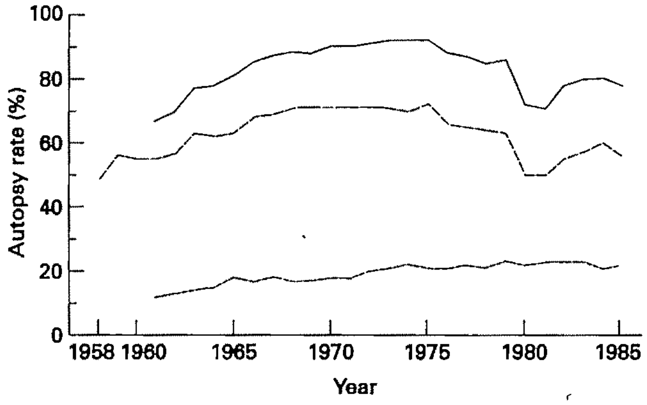

Fig. 1 Autopsy rate during 1958–1985. Total rate (———) and the individual proportions conducted by the department of pathology (— — —) and the department of forensic medicine (····) are shown

Results

Asymptomatic TAAs were diagnosed in 205 cases (109 men and 96 women) (*Fig. 2* and *Table 1*). The median age at which the aneurysm was verified at autopsy was 77·7 years for men and 85·3 for women ($P < 0.05$). TAAs which involved the aorta below the diaphragm are indicated as thoracoabdominal aneurysms in *Table 1*. Coexisting aneurysms outside the aortoiliofemoral territory were almost exclusively cerebral. Around 10 per cent of patients had aortitis; medial degeneration was rare. The different parts of the thoracic aorta affected by aneurysm involvement are shown in *Table 1*. As more than one part of the thoracic aorta could be involved, the sum of parts exceeds the number of patients.

No change was evident in the annual age-standardized occurrence of TAA in the two sexes during the period of study. The overall occurrence was calculated as 489 per 100 000 autopsies in men and 437 per 100 000 in women. The rate of thoracoabdominal aneurysms was 5·3 per cent; there was no sex difference.

A total of 63 patients died as a result of rupture (*Table 2*). The median age at rupture was 79·1 years for men and 79·8 for women. In all but four patients classical TAA was definitely present: two patients had a generalized dilatation of the entire thoracic aorta, one had microscopic signs of giant cell arteritis and another had partial dilatation of the descending thoracic aorta. The rupture was always located in the wall of the aneurysm. The age- and sex-specific incidence of fatal rupture per 100 000 is shown in *Fig. 3*. The association of death with rupture was stable over the period studied.

Table 1 Patients with asymptomatic thoracic aortic aneurysms verified at autopsy from 1958 to 1985

	Men	Women
Number	109	96
Median (range) age (years)	77·7 (58–98)	85·3 (45–109)
Thoracoabdominal aneurysm	5	6
Coexisting abdominal aortic, iliac or femoral aneurysm	43	26
Coexisting aneurysm at other locations	6	4
Multiple aneurysms of the thoracic aorta	12	5
Histological aortitis	11	11
Medial degeneration	0	2
Involvement of ascending aorta	20	16
Involvement of aortic arch	48	35
Involvement of descending aorta	55	64

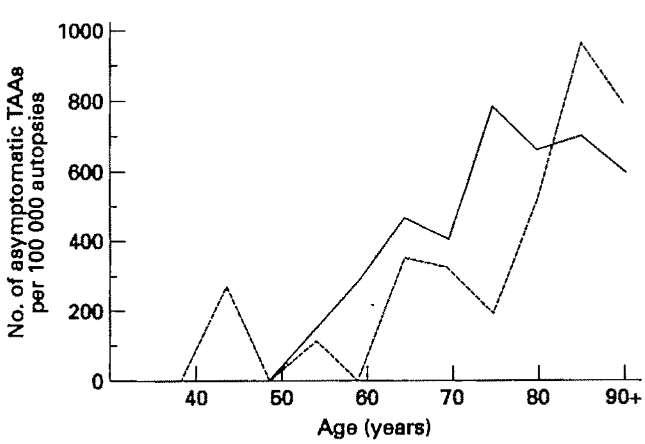

Fig. 2 Age- and sex-specific occurrence of asymptomatic thoracic aortic aneurysm (TAA) detected at autopsy performed at the department of pathology in Malmö from 1958 to 1985. ———, Men; – – – –, women

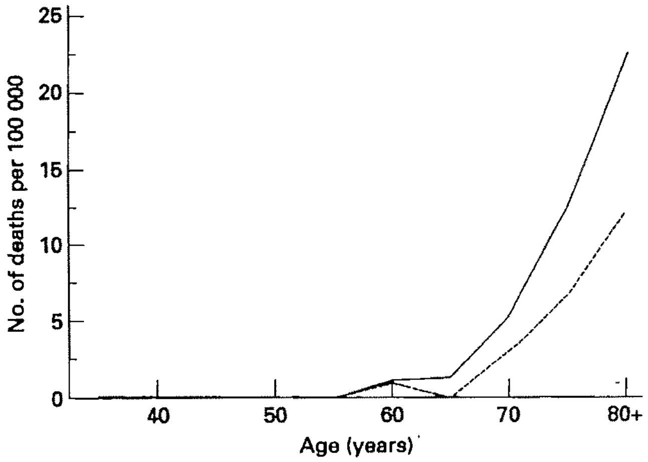

Fig. 3 Age- and sex-specific mortality rates per 100 000 from non-traumatic rupture of the thoracic aorta verified at autopsy at the departments of pathology and forensic medicine from 1958 to 1985. ———, Men; – – – –, women

Table 2 Patients with non-traumatic fatal rupture of the thoracic aorta verified at autopsy from 1958 to 1985

	Men	Women
Number	32	31
Median (range) age (years)	79·1 (62–93)	79·8 (35–92)
Thoracoabdominal aneurysm	4	6
Abdominal aortic, iliac or femoral aneurysm	9	4
Aneurysm at other locations	0	0
Multiple aneurysms of the thoracic aorta	0	2
Histological aortitis	3	5
Medial degeneration	1	1

Table 3 Patients with lethal dissection of the thoracic aorta verified at autopsy from 1958 to 1985

	Men	Women
Number	105	111
Median (range) age (years)	69·3 (28–91)	76·4 (23–98)
Aneurysm of thoracic aorta	18	26
Thoracoabdominal aneurysm	1	3
Abdominal aortic, iliac or femoral aneurysm	13	4
Aneurysm at other locations	0	0
Multiple aneurysms of the thoracic aorta	0	1
Histologically verified aortitis	5	4
Medial degeneration	26	22

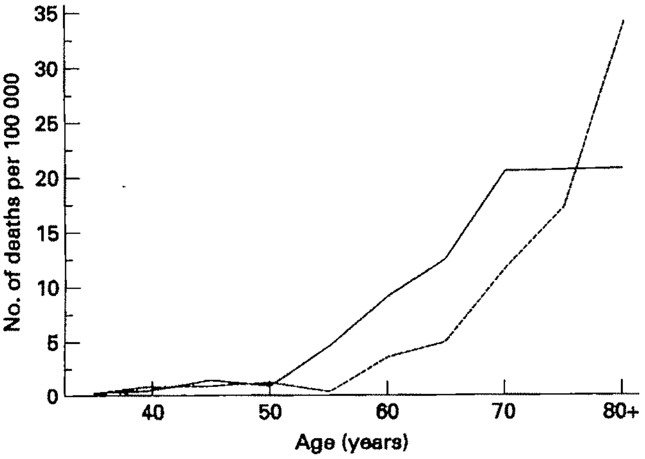

Fig. 4 Age- and sex-specific mortality rates per 100 000 from dissection of the thoracic aorta verified at autopsy at the departments of pathology and forensic medicine from 1958 to 1985. ———, Men; – – – –, women

Death as a result of dissection of the thoracic aorta was diagnosed in 216 patients (105 men and 111 women) (*Table 3*). The age at death differed significantly between the sexes ($P<0{\cdot}05$), with a median age of 69·3 years for men and 76·4 for women. Of the patients with fatal dissections, 44 also had an aneurysm. Medial degeneration was diagnosed in 48 (22 per cent) patients. This may be compared with less than 4 per cent in the group with aneurysm. Four patients in the study had Marfan's syndrome, and all had a dissection of the thoracic aorta (one man and three women). Age- and sex-specific incidence of fatal dissection was stable during the study period (*Fig. 4*). At the department of pathology 30 non-fatal dissections were registered. In *Table 4* a comparison is made with data on ruptured AAA which caused 0·6 per cent of annual deaths of men[13]. This was seven times higher than death caused by rupture of TAA and twice as common as death from dissection in men. In women, dissection was slightly more common as a cause of death than ruptured AAA.

Table 4 Number of deaths per 100 000 deaths caused by rupture of the thoracic aorta, dissection of the thoracic aorta, and rupture of abdominal aortic aneurysm. Data in part based on the study by Bengtsson and Bergqvist[13], covering the period from 1958 to 1985

	Men	Women
Ruptured thoracic aortic aneurysm	93	86
Dissection	294	343
Ruptured thoracoabdominal aneurysm	12	17
Ruptured abdominal aortic aneurysm	648	285

Discussion

To assess the prevalence of asymptomatic TAA in the population, the 'epidemiological necropsy', according to McFarlane[14], has been used in this study. Based on the high autopsy rate, the occurrence in different age groups has been considered to represent the age-specific prevalence. During the entire study period the autopsy rate remained stable and high (mean 83 per cent). The aim of autopsy at the department of forensic medicine is mainly to determine the cause of death; findings not directly related to the cause of death are not necessarily recorded. To avoid the effect of clinical bias[14] in the selection of patients for autopsy, as is probable in cases of aortic rupture and dissection, only those with asymptomatic aneurysms were included in the estimation of prevalence. The occurrence of asymptomatic TAA proved to be highest among men 75–79 years of age, whereas the peak occurrence among women appeared 10 years later. The total occurrence, however, showed no sex difference.

Coexisting extra-aortoiliac aneurysms, mostly cerebral, were found in 5 per cent of patients; this is similar to the findings of earlier studies[15,16]. About 5 per cent of the aneurysms were thoracoabdominal; there was no difference in this between the sexes. The high percentage of coexisting AAA or iliac aneurysm (39 per cent in men, 27 per cent in women) is similar to the findings of other studies[15,16], and suggests that examination of the extrathoracic aorta whenever a TAA is detected would result in several AAAs being found. Abdominal ultrasonography should be considered when surgery is contemplated.

Death as a result of dissection proved to be about three times more common than that due to rupture, and fatal dissection seemed to occur earlier in life than rupture. In the present study, dissection proved to be as common in men as women, which is in contrast to other reports[5,17]. The high autopsy rate should make the authors' data valid. The 10 per cent rate of microscopic aortitis reported here compares with the 8 per cent found by Bickerstaff *et al.*[16]. Medial degeneration was, however, significantly over-represented in the group with dissection of the thoracic aorta, 22 per cent compared with less than 4 per cent in the groups with aneurysm.

In a study using death certificate data, Lilienfeld *et al.*[5] noted a slight decline in mortality rates from aortic dissection during the period from 1968 to 1981, with death rates of around 2 per 100 000 for white men and around 1 per 100 000 for white women. Death from TAA, mainly caused by rupture, was reported as 0·7 per 100 000 for men and 0·3 per 100 000 for women, showing no change over the period of the study. In that study[5], data were based on cause of death registries, which are invalid. The autopsy rate was not given. Lilienfeld's figures are lower than the present figures of 3·2 per 100 000 and 1 per 100 000 for dissection and rupture, respectively. Similarly, no change was noted in mortality rate in either group during the period from 1958 to 1985.

Fowkes *et al.*[4] reported on hospital admissions for TAA during 1968–1983. There was a small increase in admission for TAA and aortic dissection for men, whereas the rate was constant for women. Drott *et al.*[18] found a death rate from ruptured TAA of 4 per 100 000 in a study of a Swedish population during 1952–1988. Deaths occurring outside hospital were prone to a high rate of autopsy (nearly 100 per cent); however, no rate is given for clinical autopsy.

None of the patients who underwent autopsy in Malmo had undergone operation for a TAA or a thoracoabdominal aneurysm. Operations for TAA were performed at the department of thoracic surgery in Lund, and operative activity was commenced in the middle of the 1970s. The exact frequency of patients from Malmö undergoing operation in Lund is not known, but was at most a couple of patients per year in recent years. The occurrence of thoracoabdominal aneurysm proved to be lower than expected, constituting only 5 per cent of the asymptomatic TAAs; this is similar to the 6 per cent reported by Pressler and McNamara[15]. In the present study the death rates from ruptured thoracoabdominal aneurysm were 0·1 and 0·2 per 100 000 for men and women, respectively.

In conclusion, until the middle of the 1980s the prevalence of TAA, as well as the incidence of rupture and dissection, were stable and fairly low. Surgical treatment was rare, suggesting that patients with a potentially life-threatening disease were left untreated. Owing to the infrequency of thoracoabdominal aneurysm, centralization of treatment should be discussed seriously.

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Role of cimetidine in the prevention of intimal hyperplasia in rat carotid artery

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In vitro **studies have revealed that histamine increases smooth muscle cell proliferation and migration, an effect abolished by the H_2 antagonist cimetidine. This study examined the effect of cimetidine on intimal hyperplasia *in vivo*. Thirty male Wistar rats underwent endothelial denudation of the left carotid artery; 15 received cimetidine 350 mg per kg per day for four weeks and 15 received vehicle only. Four weeks after injury the left carotid arteries were perfusion fixed and harvested. Morphometric analysis revealed that there was no significant difference between the intima:media ratio of rats treated with cimetidine (median (interquartile range (i.q.r.)) 1·69 (0·59)) and those treated with vehicle (median (i.q.r.) 1·59 (0·59), $P = 0·28$). Similarly, the percentage luminal reduction was not significantly different between the groups (median (i.q.r.) 54·7 (19·9) per cent and 45·8 (13·4) per cent respectively, $P = 0·30$). It is concluded that treatment with cimetidine does not reduce the formation of intimal hyperplasia in rat carotid arteries de-endothelialized with a balloon catheter.**

Injury to diseased or normal arteries results in a wound healing response[1]. All forms of vascular intervention cause vascular injury and, although wound healing is necessary for repair, an excessive response, or intimal hyperplasia, may result in luminal narrowing and failure of the vascular intervention. Intimal hyperplasia is responsible for restenosis after such procedures as percutaneous angioplasty, bypass grafting and endarterectomy[2–4].

Arterial injury may result in the removal of the endothelium with or without damage to the media[1]; this can be reproduced in rats by the passage of a balloon embolectomy catheter along the common carotid artery[5]. When the subendothelium of an artery is exposed, platelets adhere to it almost immediately[6]. Platelet adhesion and aggregation result in a release reaction in which the contents of the platelet α-granules are discharged. Approximately 24 h after balloon injury, a fraction of the medial smooth muscle cells commence proliferation, followed by migration from the vascular media into the intima where smooth muscle cells continue to proliferate and form a thickened intimal layer[7]. The intima is further enlarged by the accumulation of extracellular matrix synthesized by smooth muscle cells[5,7].

Platelet α-granules contain a variety of factors and several of these, notably transforming growth factor β, platelet-derived growth factor (PDGF), noradrenaline, adenosine 5'-diphosphate (ADP), serotonin and histamine, enhance smooth muscle cell migration and proliferation *in vitro*. These factors can, therefore, be implicated in the pathogenesis of intimal hyperplasia[8,9]. Using platelet factor 4 as a marker, it has been shown that platelet products can rapidly permeate through the arterial wall after de-endothelialization[10]. Although this may be a short-lived and self-limiting process, it does provide evidence that platelet products could influence arterial wall smooth muscle cells. Platelets appear to stimulate smooth muscle cell migration into the intima of the injured artery, rather than increasing their proliferation, and intimal lesion formation is reduced by thrombocytopenia[11,12]. The role of growth factors (particularly PDGF) in the pathogenesis of intimal hyperplasia has received considerable attention over the past decade; far less attention has been devoted to other platelet peptides such as histamine. Histamine increased smooth muscle cell migration *in vitro* and addition of cimetidine, an H_2 antagonist, inhibited the stimulatory effect of histamine in this system[8]. There have been no studies of the influence of cimetidine on intimal hyperplasia *in vivo*. This study tests the hypothesis that cimetidine, by inhibiting smooth muscle cell migration and to a lesser extent proliferation, is effective in preventing intimal hyperplasia in a rat model.

Materials and methods

Thirty 8-week-old male Wistar rats (290–355 g) were divided into two groups: 15 control rats received vehicle and 15 received cimetidine 120 mg/kg at 09.00 h and 230 mg/kg at 17.00 h mixed with distilled water. This dosage regimen was based on a pilot study (data not shown). Cimetidine administration was commenced 2 days before the endothelial injury and was continued until death. Both the drug and vehicle were administered to the back of the throat using a syringe attached to a 14-Fr cannula. A cimetidine assay was performed in a commercial toxicology laboratory by high-performance liquid chromatography.

Arterial injury model

A well established rat carotid artery model was used[5]. All procedures were performed using halothane inhalational anaesthesia in fully equipped animal operating theatres and in accordance with National Health and Medical Research Council guidelines for the use of laboratory animals. A midline neck incision was made and the distal left common carotid and external carotid arteries were exposed. The left external carotid was ligated distally and an arteriotomy was performed. A 2-Fr Fogarty balloon catheter (Baxter Healthcare, Old Toongabbie, New South Wales, Australia) was introduced through the arteriotomy and advanced into the proximal common carotid artery. The inflated balloon catheter was withdrawn three times to cause de-endothelialization of the artery. It was distended with a standardized volume to a fixed diameter with normal saline to allow slight resistance on passage along the common

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carotid artery. After the third pass, the catheter was removed and the external carotid artery ligated at its origin.

Histological preparation and morphometry

Four weeks after injury, the rats were anaesthetized and blood was taken for cimetidine assay. The carotid arteries were fixed by perfusion of 0·9 per cent saline for 2 min, followed by 10 per cent buffered formaldehyde for 5 min, at a pressure of 100 mmHg via the left ventricle and root of the ascending aorta. The effluent was drained via the right atrium. The left common carotid arteries were ligated at their origin and distal end, and harvested. Arteries were further fixed in formaldehyde by immersion for at least 48 h. After fixation, each artery was divided into proximal, middle and distal segments. Two 5-μm thick sections were taken from the central portion of each segment (generating six sections per specimen) and stained with haematoxylin and eosin.

Morphometric analysis was performed using a computerized image analysis system (Chromatic Image Analysis System; Leading Edge Pty, Adelaide, South Australia, Australia) at a magnification of 64 times. Using a digitizing pad to outline the constituent parts of the arterial wall the total, medial, intimal and luminal areas were measured. The mean measurements from six sections of each specimen were used. Intimal hyperplasia was also expressed as the intima:media ratio and as percentage luminal reduction, i.e. (intimal area/(intimal + luminal area)) × 100, for each section. These calculations correct for minor variation in lumen or vessel size. Morphometric measurement was performed by a single observer in a blinded fashion.

Statistical analysis

Area measurements of arteries from the cimetidine-treated and control groups were compared using the Mann–Whitney *U* test performed using a statistical package (Microcomputer Applied Statistical System, Mass 3·5; WESTAT Associates, Nedlands, Australia) with an alpha value of less than 0·05 being accepted as statistically significant.

Results

One death due to aspiration occurred in the control group at 2 weeks. The mean cimetidine level in treated rats at the time of humane killing and 2 h after the last dose was 10·6 mg/l. Typical histological findings are shown in *Figs 1* and *2*. Marked intimal thickening was seen in all injured arteries in both treated and control animals. The morphometric results for the injured arteries are shown in *Table 1*; data from the uninjured arteries are not shown.

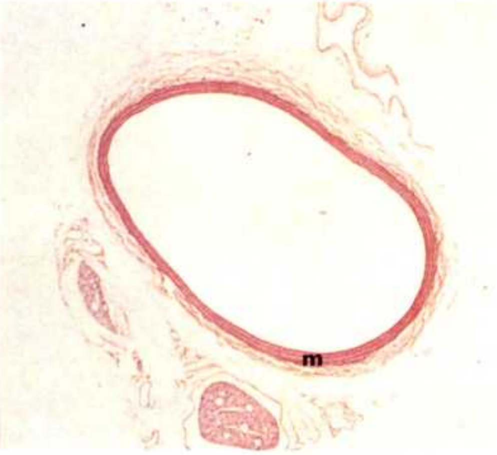

Fig. 1 Transverse section of an uninjured rat carotid artery showing media (m) and no detectable intima. (Haematoxylin and eosin stain, original magnification × 50)

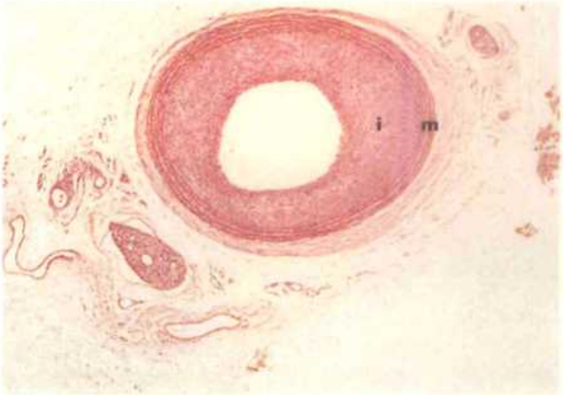

Fig. 2 Transverse section of a rat carotid artery 4 weeks after injury showing media (m) and the thickened intima (i). (Haematoxylin and eosin stain, original magnification × 50)

Table 1 Morphometric data and analysis

	Control ($n = 14$)	Cimetidine ($n = 15$)	*P*†
Total area (mm^2)	2·248 (0·307)	2·316 (0·382)	0·26
Medial area (mm^2)	0·534 (0·049)	0·561 (0·066)	0·39
Intimal area (mm^2)	0·819 (0·227)	0·947 (0·310)	0·19
Luminal area (mm^2)	0·854 (0·277)	0·766 (0·390)	0·41
Intima : media ratio	1·594 (0·587)	1·688 (0·587)	0·28
Percentage luminal reduction*	45·8 (13·4)	54·7 (19·9)	0·30

Values are median (interquartile range). *Calculated as: intimal area/(intimal + luminal area)) × 100 for each section. †Mann–Whitney *U* test.

Discussion

Intimal hyperplasia following balloon injury is due to smooth muscle cell migration, proliferation and matrix synthesis[5]. Although the role of smooth muscle cell proliferation and its control by mitogens has received considerable attention, the importance of migration should not be neglected[13]. Migration of smooth muscle cells through the internal elastic lamina is an essential step and occurs 3–4 days after injury[14]. This migration is influenced by various factors including heparin, PDGF and arterial flow[15–17]. Platelets appear to be important in this process and the size of the intimal lesion correlates with the degree of platelet aggregation[18]. Platelet products, particularly PDGF, are important in the initiation of smooth muscle cell migration[11,14]. Both thrombocytopenia and anti-PDGF antibody reduce early smooth muscle cell migration, probably by inhibiting the induction of tissue plasminogen activator expression[14]. Thrombocytopenia also inhibits intimal thickening after injury[11,12]. Although aspirin itself does not appear to inhibit intimal hyperplasia[19], clopidogrel (an ADP-selective antiplatelet drug) inhibited intimal hyperplasia 3 weeks after desiccation injury to rabbit carotid arteries[20]. There is, therefore, good evidence that manipulation of platelet function can influence intimal hyperplasia. Whether these effects are due to reduced exposure of the arterial wall to growth factors, such as PDGF, or the absence of other platelet factors is unclear.

In addition to peptide growth factors, platelets release numerous other substances including serotonin, ADP, noradrenaline, histamine, bradykinin, thromboxane A_2 and platelet activating factor[21]. These are released at sites of vascular injury, diffuse into the vessel wall, and have the potential to influence smooth muscle cells within the wall[8,10]. *In vitro* studies have shown that histamine increases smooth muscle cell proliferation by 11 per cent and migration by 38 per cent[8]. This effect was inhibited by the H_2 antagonist cimetidine, but not by H_1 blockade using diphenhydramine[8]. Furthermore, histamine, in addition to serotonin and ADP, potentiated the mitogenic effect of PDGF, suggesting that these platelet products may act as amplification factors[9]. Interestingly, histamine stimulates the proliferation of airway smooth muscle cells[22] and rectal tubulovillous polyp cells *in vitro*; this effect is also inhibited by cimetidine[23].

On the basis that cimetidine could inhibit smooth muscle cell migration, and possibly proliferation, the influence of this agent on intimal thickening following balloon injury to the rat carotid artery was examined. There was no significant difference in intimal area or lumen reduction between the control and cimetidine-treated animals (*Table 1*). The chance of demonstrating a pharmacological effect was maximized by using a high dose and starting the drug 48 h before inducing the injury. The dose of cimetidine used in rats in this study was 350 mg per kg per day to maintain a blood level exceeding 0·5 mg/l, a level considered to be therapeutic in humans.

It is possible that the effects of histamine on smooth muscle cells *in vitro*[8] were pharmacological, and that histamine is not important in the control of smooth muscle cell migration and proliferation following balloon injury. If, however, histamine is important in early smooth muscle cell migration, a difference may have been detectable at an early time point (e.g. 7 days), and the lack of effect at 4 weeks may be explained by the dominance of smooth muscle cell proliferation and matrix synthesis at the later time. In other words, early inhibition of migration may not alter the final outcome, as suggested by the observation that thrombocytopenia (at the time of injury) inhibited intimal thickening at 1 but not at 2 weeks after injury[11]. The influence of cimetidine on smooth muscle cell migration (an early event) was not assessed in this study; the later time point was chosen as it is inhibition of the established intimal lesion that is of clinical relevance. The results of this experimental study do not support further assessment of H_2 receptor blockade in intimal hyperplasia.

Acknowledgements

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Importance of human immunodeficiency virus-associated lymphadenopathy and tuberculous lymphadenitis in patients undergoing lymph node biopsy in Zambia

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The relative importance of human immunodeficiency virus (HIV)-associated lymphadenopathy amongst patients presenting for lymph node biopsy in Central Africa is unknown. HIV-1 serology and histology of patients undergoing superficial lymph node biopsy during 1989–1990 in Lusaka, Zambia, were examined in a prospective cohort study of HIV serology and by retrospective review of laboratory records. Of 727 lymph nodes biopsied in Lusaka in 1989–1990, 380 (52 per cent) showed tuberculous lymphadenitis, 160 (22 per cent) histology suggestive of primary HIV lymphadenopathy and 66 (9 per cent) nodal Kaposi's disease. HIV serology was tested in 280 adults and was positive in 91 per cent (255 patients), including 89 per cent (153 of 171) of those with tuberculous lymphadenitis, 98 per cent (63 of 64) of those with histology suspicious of primary HIV lymphadenopathy and all (24 of 24) with nodal Kaposi's disease. Other HIV-associated lymphadenopathy included nodal lymphomas and lymphoepithelial cysts. HIV serology was tested in 22 children and was positive in eight, including four of 14 with tuberculous lymphadenitis. It is concluded that HIV-associated lymphadenopathy, especially tuberculous lymphadenitis, is very common amongst patients presenting for lymph node biopsy in Central Africa.

Human immunodeficiency virus (HIV) infection was recognized in Zambia in 1983[1] and by 1989–1990 had become a serious national health problem[2–4] with an estimated infection rate of over 40 per cent in high-risk groups and over 10 per cent in low-risk groups[4]. HIV-infected patients with symmetrical generalized lymph node enlargement do not usually require surgical biopsy[5,6], but in Africa HIV-associated tuberculosis is common[7–9] and many patients are referred for lymph node biopsy to exclude tuberculous lymphadenitis. The resulting effect of the HIV epidemic on surgical lymph node biopsies in Central Africa has not been studied. The present study tested a cohort of patients who underwent lymph node biopsy in Lusaka during 1989–1990 for HIV-1 infection and reviewed the histology of all superficial lymph nodes biopsied in Lusaka over the same period.

Patients and methods

Patients who attended for biopsy of a superficial lymph node at the University Teaching Hospital, Lusaka, under the care of one of the authors (C.B.) during 1989–1990 and who consented to HIV testing were included in a prospective study of lymph node pathology. Lymph node biopsy was carried out at the request of the referring clinician for diagnostic purposes. Cooperation with the chest clinic produced a bias towards patients with suspected tuberculous lymphadenitis. A change in recruitment to the study excluded those under 17 years of age during 1990.

Immediately before lymph node biopsy, blood was drawn for HIV analysis and was subsequently tested for the presence of HIV-1 antibody by competitive recombinant enzyme-linked immunosorbent assay (ELISA) (Wellcozyme Recombinant; Wellcome Diagnostics, Dartford, UK). Half of each biopsy specimen was sent for mycobacterial culture and half for histopathological examination. All histological specimens were examined in Lusaka by one of the investigators (P.S.P.) and were reported without knowledge of the patient's HIV serology. Additional histological examination was carried out on selected specimens in Belfast (H.B.). Histology was considered to be suspicious of primary HIV lymphadenopathy if it showed typical follicular and interfollicular patterns[10–12]. Non-specific lymphadenitis refers to inflammatory or involutional changes with no specific features to suggest either primary HIV lymphadenopathy or tuberculous lymphadenitis.

After completion of this study, all information on other superficial lymph nodes biopsied in Lusaka during 1989–1990 was retrieved from the records of the Department of Histopathology of the University Teaching Hospital, which examines all histological material in the city. Lymph nodes removed together with a primary tumour were excluded from analysis.

Results

A total of 727 patients underwent superficial lymph node biopsy in Lusaka during 1989–1990, of whom 591 (81 per cent) were adults, 126 (17 per cent) were children and ten (1 per cent) could not be identified from the records as either an adult or child. The histological results, age and sex of these patients are presented in *Table 1*. Tuberculous lymphadenitis was the most common diagnosis in both adults and children.

Some 302 patients undergoing lymph node biopsy were tested for HIV serology. These patients included 52 per cent (154 of 297) of adults undergoing lymph node biopsy in Lusaka in 1989, 43 per cent (126 of 294) of adults in 1990 and 29 per cent (22 of 75) of children in 1989. Ninety-one per cent of adults were HIV antibody positive, including 89 per cent of adult cases of tuberculous lymphadenitis (*Table 2*). Two HIV antibody positive adults showed double nodal pathology, namely tuberculous lymphadenitis with nodal Kaposi's disease and lymphoma respectively. Of five HIV antibody-positive patients with lymphoma, three had high-grade lymphomas, one a low-grade lymphoma and one a mixed cellularity Hodgkin's lymphoma. A 22-year-old woman with lymphadenopathy secondary to metastatic right colonic carcinoma was HIV

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positive. Eight of 22 children were HIV antibody positive, of whom five were aged 15 or 16 years. Two of the patients with lymphoepithelial cysts have been reported previously[14].

The sex and age distribution of patients undergoing lymph node biopsy with known and unknown HIV serology were similar. The age distribution of adults with tuberculous lymphadenitis, histology suspicious of primary HIV lymphadenopathy and nodal Kaposi's disease, with known and unknown HIV serology, is shown in *Figs 1* and *2* respectively.

Results of mycobacterial culture were available for 182 cases of tuberculous lymphadenitis included in the prospective study; *Mycobacterium tuberculosis* was grown from 99 patients (54 per cent). Positive culture rates were similar for patients with HIV-positive (85 of 154 (55 per cent)) and HIV-negative (14 of 28 (50 per cent)) tuberculous lymphadenitis. No *M. bovis* and no non-tuberculous mycobacteria were grown.

Table 1 Histology of superficial lymph node biopsies in Lusaka, 1989–1990*

	No of patients†	Mean (range) age (years)	Sex ratio (M:F)
Adults (>16 years; *n* = 591)‡			
Tuberculous lymphadenitis	315 (53)	30·8 (17–64)	162:152¶
Histology suspicious of primary HIV lymphadenopathy	132 (22)	30·2 (17–61)	59:73
Nodal Kaposi's disease[13]	52 (9)	30·0 (18–52)	35:17
Non-specific lymphadenitis	48 (8)	34·0 (17–74)	23:25
Nodal lymphoma	23 (4)	37·0 (18–67)	13:10
Metastatic lymphadenopathy	19 (3)	48·3 (19–68)	8:11
Lymphoepithelial cyst[14,15]	3 (1)	26·0 (18–33)	0:3
Castleman's disease§	1 (0)	27	0:1
Children (0–16 years; *n* = 126)			
Tuberculous lymphadenitis	59 (47)	7·3 (0–16)	27:28¶
Histology suspicious of primary HIV lymphadenopathy	26 (21)	5·4 (0–16)	13:12¶
Non-specific lymphadenitis	20 (16)	5·8 (1–15)	8:12
Nodal Kaposi's disease	14 (11)	6·5 (1–15)	8:4¶
Nodal lymphoma	6 (5)	8·7 (4–16)	5:1
Metastatic lymphadenopathy	1 (1)	8	1:0

*Excludes ten patients whose age was not known (tuberculous lymphadenitis, six patients; suspicion of primary human immunodeficiency virus (HIV) lymphadenopathy, two; non-specific lymphadenitis, two). †Values in parentheses are percentages. ‡A total of 591 adults with 593 diagnoses, two patients showing double nodal histology: tuberculous lymphadenitis with Kaposi's disease and lymphoma respectively. §Angiofollicular hyperplasia[16]. ¶Sum does not equal number of patients as sex unknown in some cases

Table 2 Human immunodeficiency virus 1 serology of patients undergoing superficial lymph node biopsy in Lusaka, 1989–1990*

	No. of patients	HIV positive
Adults (>16 years)	280†	255 (91)
Tuberculous lymphadenitis	171 (61)	153 (89)
Histology suspicious of primary HIV lymphadenopathy	64 (23)	63 (98)
Nodal Kaposi's disease[13]	24 (9)	24
Nodal lymphoma	8 (3)	5
Non-specific lymphadenitis	7 (3)	7
Metastatic lymphadenopathy	4 (1)	1
Lymphoepithelial cyst[14,15]	3 (1)	3
Castleman's disease‡	1 (0)	1
Children (0–16 years)	22	8
Tuberculous lymphadenitis	14	4
Histology suspicious of primary HIV lymphadenopathy	4	3
Nodal Kaposi's disease	1	1
Nodal lymphoma	2	0
Metastatic lymphadenopathy	1	0

Values in parentheses are percentages: percentages in the first column are of adults or children respectively; percentages in the second column are of the corresponding figure in the first. *Children only tested during 1989. †A total of 280 adults with 282 diagnoses, two patients showing double nodal histology: tuberculous lymphadenitis with Kaposi's disease and lymphoma respectively (both human immunodeficiency virus (HIV) positive). ‡Angiofollicular hyperplasia[16]

Discussion

The present study shows the importance of HIV-related lymphadenopathy to surgeons working in Central Africa. It indicates the particular importance of secondary HIV lymphadenopathy in the form of tuberculous lymphadenitis. Of adults undergoing lymph node biopsy who

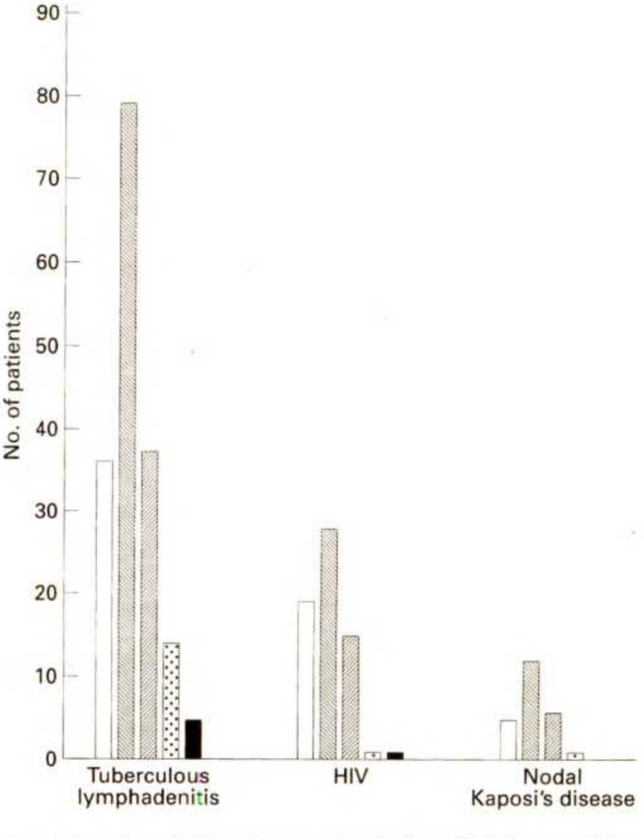

Fig. 1 Lymph node biopsies: age distribution of adults tested for human immunodeficiency virus infection. □, Age 17–24 years; ▨, 25–34 years; ▨, 35–44 years; ▨, 45–54 years; ■, 55 or more years. HIV, histology suspicious of primary human immunodeficiency virus lymphadenopathy

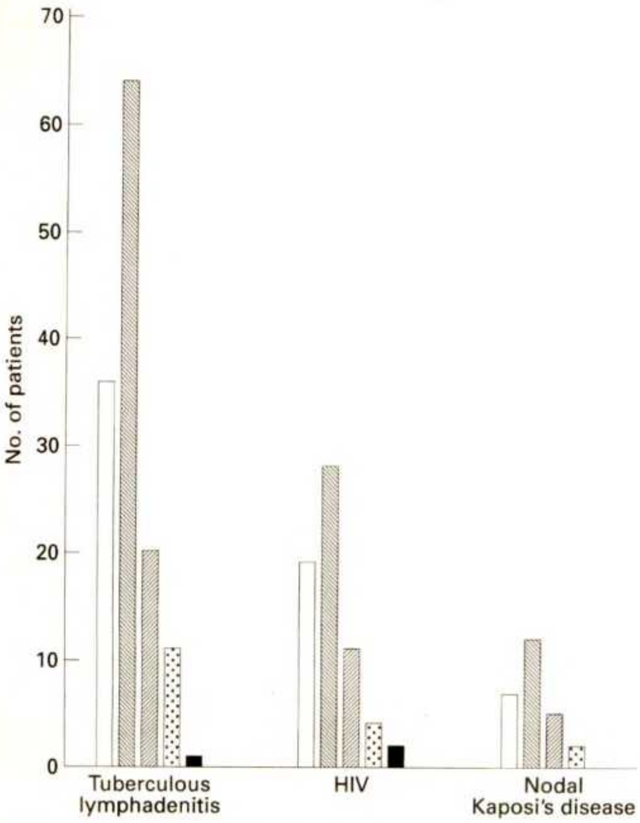

Fig. 2 Lymph node biopsies: age distribution of adults not tested for human immunodeficiency virus infection (age not available for 18 patients). □, Age 17–24 years; ▨, 25–34 years; ▨, 35–44 years; ⬚, 45–54 years; ■, 55 or more years. HIV, histology suspicious of primary human immunodeficiency virus lymphadenopathy

were tested for HIV antibodies, 91 per cent were HIV positive and, of these, 60 per cent had HIV-associated tuberculous lymphadenitis. Other HIV-related lymphadenopathy included nodal lymphoma[12] and lymphoepithelial cysts[14,15]. In children lymphadenopathy was less likely to be HIV related except amongst adolescents.

Studies of HIV-associated lymphadenopathy have concentrated on the pathology of primary HIV lymphadenopathy[10–12], as secondary HIV lymphadenopathy is uncommon in Western medical practice[17–19]. The pathology of HIV-associated lymphadenopathy presenting for biopsy in Africa has not been reported previously. Recent surveys of lymph node biopsies in Malawi (1985–1988)[20] and in Tanzania (1984–1988)[21] excluded investigation of HIV serology. Studies and reviews of HIV-associated tuberculosis in Africa have included few patients with tuberculous lymphadenitis[7,9]

In the present study 42 per cent of patients undergoing lymph node biopsy during 1989–1990 in Lusaka were examined for HIV infection with Wellcozyme ELISA. Although a single test was used, as is common in Africa, Wellcozyme ELISA is of proven sensitivity and specificity in Africans[22,23]. HIV-2, which is present in west Africa[24], had not been identified in Zambia up to the end of 1992 (National AIDS Surveillance, Zambia, personal communication). The age and sex profile of adults tested for HIV infection was similar to that of those not tested for HIV infection (*Figs 1* and *2*).

The high incidence of HIV infection amongst patients undergoing lymph node biopsy in Lusaka reflects the high prevalence of both HIV infection[4] and tuberculosis[8] in Central Africa. It is estimated that 45 per cent of the population of sub-Saharan Africa has been infected with tuberculosis[8] and clinical tuberculous disease occurs in at least 40–50 per cent of persons with dual HIV–tuberculosis infection[7–9]. HIV-associated tuberculosis is more frequently extrapulmonary than is classical HIV-negative tuberculosis[7,9].

A minority of HIV-positive patients undergoing lymph node biopsy had primary HIV lymphadenopathy, reflecting the selection of patients for biopsy, as routine biopsy of HIV-positive patients with palpable lymph nodes is unnecessary[5,6]. Primary HIV lymphadenopathy corresponds to the clinical condition of persistent generalized lymphadenopathy[25]. Histology is often highly suggestive[11,12] but as there is overlap with other conditions the diagnosis must be confirmed by HIV testing.

Fifty-two per cent of patients undergoing lymph node biopsy in Lusaka in 1989–1990 had tuberculous lymphadenitis. This proportion is higher than in studies from Africa before the emergence of acquired immune deficiency syndrome (AIDS) (previously 15–45 per cent)[26–28]. There was also a much higher proportion of adult to child cases of tuberculous lymphadenitis (5:1) than in pre-AIDS Africa (previously in the range of 1:1 to 2:1)[27–30]. The high HIV-seropositivity rate amongst adult cases in Lusaka explains this finding (*Table 2*). Failure to grow non-tuberculous mycobacteria confirms the rarity of infection with these micro-organisms in patients both with and without AIDS in Africa[30–32].

Adult nodal Kaposi's disease was invariably HIV associated and displayed the male predominance characteristic of this disease in Africa[33]. Children with nodal Kaposi's disease undergoing lymph node biopsy, none of whom were tested for HIV, may represent endemic Kaposi's disease[34] as Kaposi's disease is uncommon in HIV-infected African children[35].

In showing the importance of tuberculous lymphadenitis as a cause of HIV-associated lymphadenopathy in Zambia, the study emphasizes that HIV-positive patients with suspicious asymmetrical nodes in central Africa should be investigated further. The clinical distinction between primary and secondary tuberculous HIV lymphadenopathy is, however, not always as clearcut in Africa as it is in the West, and the index of suspicion for tuberculous lymphadenitis should be low. In the present study, 12 per cent of HIV-positive adults with tuberculous lymphadenitis had small symmetrical nodes[36]. The study supports the need for simple, appropriate methods, such as wide-needle aspiration[37], for the diagnosis of tuberculous lymphadenitis in a region where facilities for surgery and especially for histopathology are often scarce. It is also probable that the importance of HIV-associated tuberculous lymphadenitis demonstrated in the study will be reflected in the developing HIV epidemic in India and south-east Asia[38], which share with Africa the problem of endemic tuberculosis.

Acknowledgements

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Real and apparent mortality from congenital diaphragmatic hernia

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Some 50 cases of congenital diaphragmatic hernia (CDH) born in the authors' regional referral area over the 14 years from 1980 to 1993 were reviewed, contrasting 7 years when management included preoperative ventilatory stabilization with the preceding 7 when urgent surgery was performed. Six children experienced no respiratory distress and suffered no mortality. For infants with respiratory distress in the first 6 h of life, ventilatory stabilization improved survival rates of those who reached the surgical centre from 45 per cent between 1980 and 1986 to 59 per cent between 1987 and 1993. A larger proportion of the total number of patients, however, continued to die without reaching the surgical centre. The improvement in survival rate based on the true incidence of CDH was from 28 per cent in the first period to 38 per cent in the second. The apparent poor survival rate of patients born in central obstetric units compared with those born in peripheral units (37 *versus* 75 per cent) can be attributed to patient selection; a larger number of children born in central units were transferred for surgery (70 *versus* 57 per cent). There is no evidence that paediatricians have altered their referral practice to include prolonged ventilation outside the surgical unit since delayed surgery was advocated. Assessment of the impact of altering the management of CDH cannot be made without knowing the number of patients who die before transfer to a neonatal surgical unit. Any serious attempt to reduce the mortality rate of CDH must be directed to neonates who are not presently referred to the surgical service.

The optimal management of congenital diaphragmatic hernia (CDH) remains controversial, with continued high mortality rates. Although there is interest in extracorporeal membrane oxygenation (ECMO) for infants with severe lung hypoplasia[1,2], the benefits of this therapy are as yet unproven[3].

Since 1987 the importance of ventilatory stabilization before operation has become apparent[4], and there has been increased appreciation of the merits of delayed surgical repair either with[5] or without[6] ECMO, although not all groups have been able to demonstrate improved survival[7,8]. The results of delayed surgery for CDH over the years 1987–1993 inclusive are compared with those of the preceding 7 years when urgent surgery was performed.

This department is a referral centre for geographically remote obstetric units and those within the city of Edinburgh, UK. Any intrinsic benefit in delay between birth and surgery might be apparent among infants born in peripheral units, who usually have an enforced period of ventilation before and during transfer. Patients were analysed therefore with regard to their place of birth.

In 1978, Harrison *et al.*[9] drew attention to the 'hidden mortality' of infants with CDH who died before referral to a surgical centre. The high mortality rate reported by Harrison and colleagues has been disputed by others, who believe that a large proportion of these early deaths are associated with concomitant fatal anomalies[10]. In addition to the patients with CDH who were treated in the authors' institution, an attempt was made to discover all patients with this condition born in the referral area over the years 1980–1993 inclusive, from the records of the cause of death of the Registrar General Office for Scotland. The present report details the true incidence and mortality rate of CDH, including those who do not reach the regional neonatal surgical centre.

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Patients and methods

The records of all children with CDH admitted to the Royal Hospital for Sick Children between 1980 and 1993 inclusive were retrieved. Details extracted for all patients included age of the child at onset of symptoms, presence of respiratory distress, the need for ventilatory support before surgery, side of the hernia and time of death. This hospital serves not only the city of Edinburgh, but also geographically distant areas including Fife and the Borders of Scotland, thus the place of birth of the child and the time taken from birth to arrival in theatre were also recorded.

Since 1987 the surgical policy has been to delay surgery until the child's ventilatory index (mean airway pressure × ventilatory rate) is less than 1000. Previously, infants were taken to theatre expeditiously for emergency repair of the diaphragmatic defect.

Death certificates held by the Registrar General Office for Scotland were searched to ascertain whether there were patients with diaphragmatic hernia who had died before arrival at the hospital. The records for Edinburgh, Fife and the Borders were scanned using the International Classification of Diseases code 7966, for CDH as the primary cause of death, and also for those where diaphragmatic hernia was mentioned but not as the primary cause.

Results

Some 34 children with diaphragmatic hernia were admitted to the Royal Hospital for Sick Children; 28 with respiratory embarrassment were diagnosed within 6 h of birth. Of the six infants without respiratory embarrassment, two were asymptomatic and CDH was detected within 24 h of birth at routine examination by the presence of a right-sided apex beat and bowel sounds within the chest respectively. Each had operations within 24 h. The remaining four presented with vomiting between 2 and 8 months of age, and underwent elective surgery. There was no mortality within this group of children, who represented a different therapeutic problem and were not considered further for the purposes of this study.

Infants who presented with immediate respiratory distress

Among the 28 infants who presented with respiratory distress within 6 h of birth, 13 died, giving an overall survival rate of 54 per cent. There were 20 left-sided hernias, seven right-sided and one bilateral. Six babies with right-sided hernias, and six with left-sided hernias died, as did the infant with bilateral hernia: the higher mortality rate of right CDH was significant (P = 0·01, Fisher's exact test). There were 19 boys and nine girls but no difference in mortality rate between the sexes; 11 of the boys and four of the girls survived (P = 0·2, Fisher's exact test).

The effect of the altered policy towards the management of CDH becomes apparent when the delay before operation is analysed according to the two periods 1980–1986 and 1987–1993. One child in the second period did not improve sufficiently to allow operation, but of the remaining 27 who had operations, the median time from birth to surgery between 1980 and 1986 was 5 h, while between 1987 and 1993 it was 11·3 h (P = 0·0007, Mann–Whitney U test). Mortality during surgery also decreased; only five of 11 patients survived between 1980 and 1986, while ten of 17 survived between 1987 and 1993 (P = 0·24, Fisher's exact test) (*Fig. 1*).

Sixteen of the infants were born in one of the three maternity units within Edinburgh, while 12 were born in peripheral units in Fife, the Borders or West Lothian. While ten infants born within the city died, only three of those born in the periphery did not survive. The difference in mortality rate between the city and the peripheral units was significant (P = 0·047, Fisher's exact test). Babies born in peripheral maternity units took longer to reach the operating theatre of the children's hospital, but the difference was not significant (median time for city births 5·7 h, and for those from peripheral units 8·2 h, P = 0·4, Mann–Whitney U test). No infant's condition deteriorated during transit, and patients who were transferred and subsequently died lived for more than 24 h.

Two deaths were not directly attributable to pulmonary hypoplasia. In one patient an arterial partial pressure of oxygen ($P\mathrm{ao}_2$) of 17·1 kPa and arterial partial pressure of carbon dioxide ($P\mathrm{aco}_2$) of 5·6 kPa were achieved 6 h after surgical repair, but the child developed a tension pneumothorax, suffered cardiac arrest and had extensive neurological damage. The second patient died during surgery as a result of aspiration from a concomitant tracheo-oesophageal fistula when the abdominal viscera were returned to the abdomen. Each death occurred in the period when delayed surgery was practised.

Infants who died from congenital diaphragmatic hernia but did not reach the surgical centre

In addition to the 28 babies who were referred to the Royal Hospital for Sick Children, a further 16 who died from CDH between 1980 and 1993 in Fife, West Lothian, the Borders and Edinburgh were identified from the records of the General Registrar Office for Scotland (*Fig. 1*). When these children are added to those who reached the referral centre, the survival rate for CDH in south east Scotland is reduced to 34 per cent. Between 1980 and 1986, 11 of 18 infants born with CDH reached the hospital, while between 1987 and 1993, 17 of 26 babies with CDH reached the hospital. The proportion who reached hospital was unchanged in the two periods. Of the 16 neonates who died, four survived for less than 1 h, ten for 1–23 h and two for 1–6 days.

Babies who survived for more than 1 day but were not referred were subject to deliberate decisions to withhold active treatment because of severe associated anomalies.

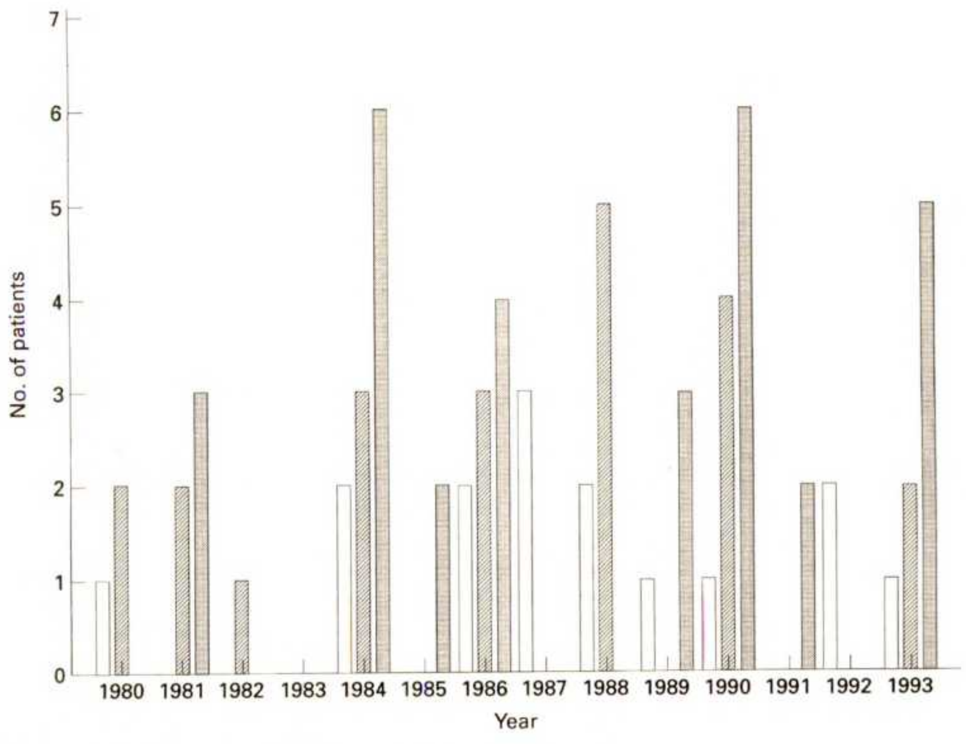

Fig. 1 Mortality of infants within, ▨ and outwith, ☐ the surgical centre; ☐, survivors

Over the study period, 17 of 23 babies born in Edinburgh maternity units died, while 12 of 21 born in peripheral units died ($P = 0{\cdot}1$, Fisher's exact test). There was no reduction in the proportion of infants referred to the surgical unit in the two 7-year intervals. Seventy per cent of infants born in central obstetrical units were transferred *versus* 57 per cent of peripheral births. The diagnosis of CDH was made on seven occasions through the use of antenatal ultrasonographic screening, although none of these children survived.

Discussion

The survival rate for babies with CDH who reached the authors' institution over the 14 years from 1980 to 1993 is 54 per cent. The policy of delayed surgery has improved the survival rate from 45 to 59 per cent in two consecutive 7-year intervals. The difference was not statistically significant, possibly because of the small size of the series, although others agree that delayed surgery is safe[7]. Delayed surgery may allow the newborn infant to avoid the decrease in respiratory compliance concomitant with immediate operation[5,11]. In one large series it was not possible to demonstrate an advantage[3], although others have suggested a trend towards better survival from delayed surgery[12]. The results achieved in surgery for CDH largely reflect patient selection, although this has been ignored in some recent reports[3–7,13–16]. The policy of delayed operation might lead to some children being detained in paediatric neonatal units for ventilation without surgical assessment, but this fear appears unfounded. The proportion of infants being referred was unchanged over the study period.

Between 1969 and 1975, Harrison *et al.*[9] identified babies born with CDH who failed to reach the main neonatal surgical centre in Norway, and calculated the 'true' mortality rate as 66 per cent. Over the 14 years reported here, 28 infants reached the regional neonatal surgical centre, while 16 died in obstetric units. The 'true' mortality rate is not 46 per cent of operated cases, but 66 per cent of all those born in the authors' referral region. The survival rate for patients who reached the surgical unit has improved, but the true mortality has not altered; 13 of 18 babies died between 1980 and 1986 and 16 of 26 died between 1987 and 1993, with seven of the initial 13 and nine of the subsequent 16 dying outwith the regional surgical centre. Ventilatory stabilization improved the survival rate, but made no impact on the infants who died soon after birth. Antenatal diagnosis and delivery of the child in a regional neonatal surgery centre has little effect on the survival of neonates with severe pulmonary hypoplasia[17–19]; the mortality rate in antenatally diagnosed cases was 100 per cent in this study. Experience of ECMO in patients diagnosed before birth does not suggest that this will lead to a significant decrease in mortality[20].

The results of surgical therapies can be analysed objectively only if the detail of patient selection is reported. Series that describe the results of antenatal diagnosis may represent the real mortality rate, as may reports such as the present one where the 'true' mortality in the referral population was calculated (approximately 66 per cent[9]). Studies that report only patients reaching their institution must be subject to the bias of case selection. CDH is an uncommon condition and few series amount to more than 100 patients, thus being liable to distortion by selection. A proportion of infants born with CDH cannot be managed by current treatment, early death occurring as a result of other life-threatening anomalies[17,21].

In the present study there was a survival advantage for babies born in outlying units compared with those born within Edinburgh. This cannot be explained by a longer period of preoperative ventilation, as the differences were insubstantial. This finding may be an artefact caused by case selection, and emphasizes the need for careful interpretation of apparent differences in survival in infants born with CDH.

Mortality appears to be decreasing among infants surviving to be operated on using a policy of delayed surgery, but there remains a continued high, hidden mortality among neonates who die shortly after birth. There seems little prospect of current, or new, modes of therapy reducing this, as treatments such as ECMO are restricted to babies who reach a regional neonatal surgical unit. There was no evidence that paediatricians are altering their referral practices to encompass preoperative ventilation outside a surgical neonatal unit, and there seems no real difference between the survival of infants born in central or peripheral obstetric units.

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Management options in vertebral artery injuries

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The treatment of 22 patients with vertebral artery injuries was reviewed. Only four patients required an emergency operation. Most of the injuries (13 of 22) were successfully managed by observation. Five patients were managed by angiographic embolization which was successful in three. In three patients with an aneurysm and arteriovenous fistula, proximal embolization of the vascular lesion was not adequate and a suboccipital craniectomy was required for distal ligation. Most vertebral artery injuries can safely be managed without an operation, or by angiographic embolization. Surgical intervention should be reserved for patients with severe bleeding or where embolization has failed.

Vertebral artery injuries are being recognized with increased frequency, because of the greater number of penetrating neck wounds and the more liberal use of diagnostic angiography. The surgical exposure of vertebral artery injuries is technically challenging and is one of the most difficult procedures in trauma surgery. Improvements in interventional radiology and increased non-operative management of occult vascular injuries, have changed the treatment of the injured vertebral artery. In this study the role and effectiveness of the various existing therapeutic modalities are reviewed and a management protocol for complicated vertebral artery injuries is suggested.

Patients and methods

The treatment of 22 patients with vertebral artery injuries treated at the Los Angeles County and University of Southern California Medical Center between 1990 and 1994 was reviewed. In 12 patients the data were obtained from the trauma registry and chart review. In the remaining ten patients data were prospectively collected as part of an ongoing study on penetrating neck injuries. During the study, the policy was to perform routine angiography for all haemodynamically stable patients with neck trauma, irrespective of the region of injury. Most injuries were due to gunshot wounds (18 patients); only four patients had knife injuries. There were 21 men and one woman, with a mean age of 25 (range 14–42) years.

The most common clinical findings on admission included hypotension (11 patients), a moderate or large haematoma (nine), active bleeding (six) and a bruit (three). Four patients were asymptomatic.

Thirteen patients had vertebral artery injuries with no other vascular trauma. Four of these were asymptomatic, seven had signs diagnostic of vascular injury (three bruits, two expanding haematomas, two severe active bleeding) and two had suggestive signs (stable haematoma, mild hypotension). No patient in this series had neurological signs related to vertebral artery injury.

Fifteen patients had major associated neck injuries, to the common carotid (two), internal carotid (two), internal jugular vein (two), subclavian artery (one), internal mammary artery (one), spinal cord (seven), brachial plexus (two), pharynx (three) and there was one oesophageal perforation.

Four of the 22 patients had an emergency operation without angiography because of bleeding and shock. The remaining 18 patients had angiography (*Table 1*).

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The vertebral artery lesions were managed conservatively in 13 patients. This group included one with bilateral vertebral artery thrombosis (*Fig. 1*), another with thrombosis of one vertebral artery and dissection of the other, and a third patient with ipsilateral vertebral artery and common carotid artery occlusions. There were no neurological symptoms in these patients. Three patients had vascular repair of associated injuries to the internal carotid or subclavian arteries but no attempt was made to operate on the occluded vertebral artery. One patient in this group had a vertebral artery intimal tear and a small ipsilateral internal carotid pseudoaneurysm. This patient was successfully managed by observation. Repeat angiography 1 month after the injury showed a normal vertebral artery and a stable carotid lesion.

Five patients were managed by angiographic embolization which successfully controlled active bleeding and a false

Table 1 Angiographic findings in 18 patients

Vertebral artery occlusion	12
Unilateral vertebral artery occlusion	6
Bilateral vertebral artery injuries	2
Associated carotid injuries	2
Associated subclavian injuries	1
Associated vertebral artery aneurysm	1
Vertebral artery aneurysm with arteriovenous fistula	3
Vertebral artery transection with active bleeding	2
Vertebral artery intimal tear	1
Total	18

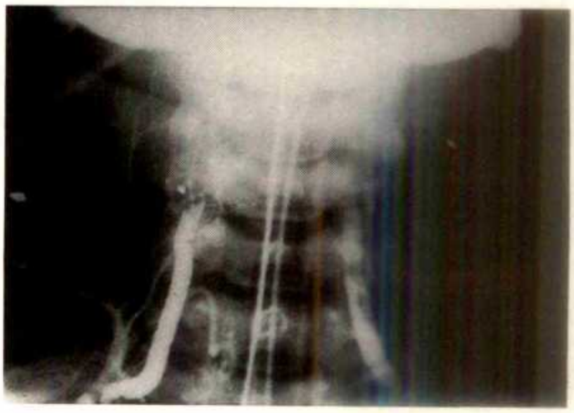

Fig. 1 Bilateral vertebral artery thrombosis. The patient had no neurological problems

aneurysm with arteriovenous fistula (AVF) in two patients (*Fig. 2*). In three patients with vertebral artery pseudoaneurysm and/or AVF, proximal embolization failed to control the problem because of the retrograde supply of the vascular lesions. A suboccipital craniectomy with distal ligation of the vertebral artery and involved veins was required to control the high AVF (*Fig. 3*). Four patients required emergency operation without angiography because of active bleeding and haemodynamic

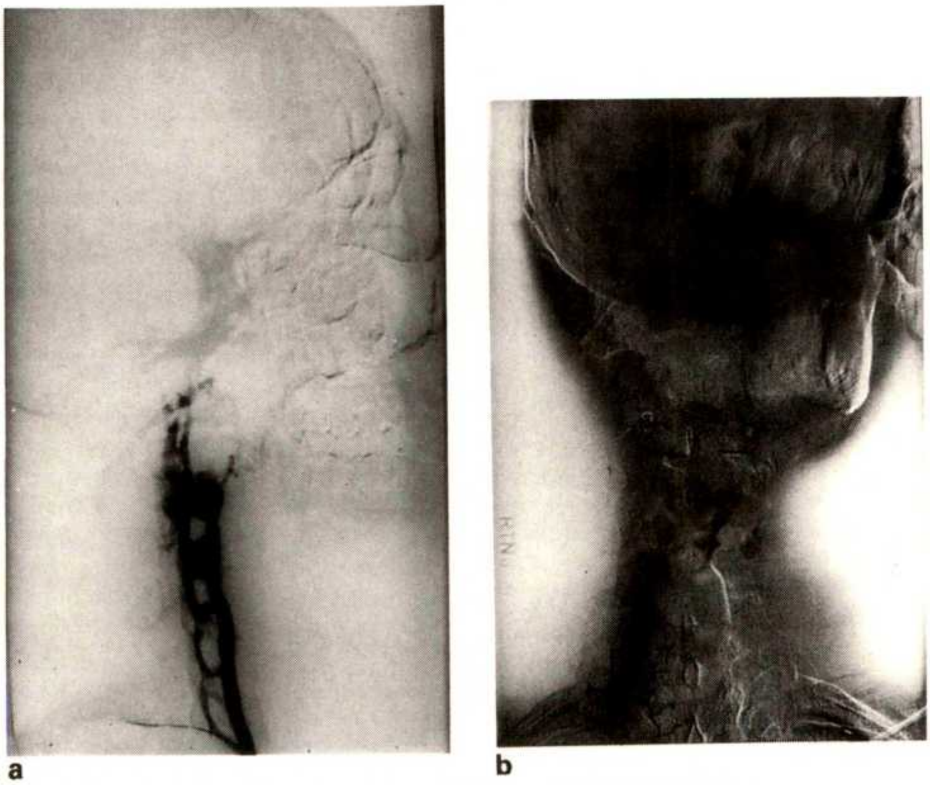

Fig. 2 Vertebral artery false aneurysm with arteriovenous fistula **a** before and **b** after embolization

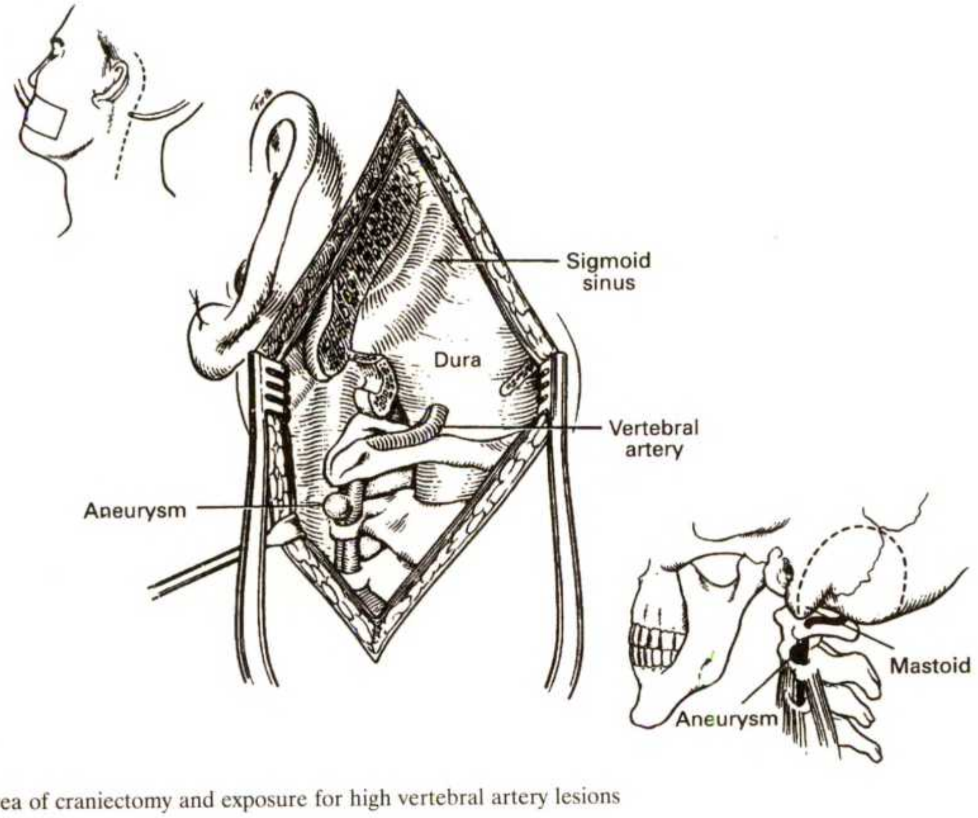

Fig. 3 Incision, area of craniectomy and exposure for high vertebral artery lesions

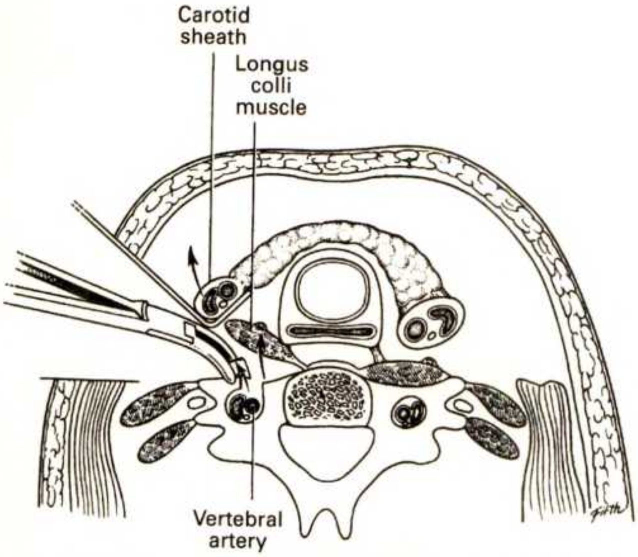

Fig. 4 Surgical approach to the vertebral artery in the vertebral canal. The carotid sheath was retracted medially and the longus colli muscle swept off the bone. The anterior rim of the vertebral canal was removed with bone nibblers and the vertebral artery exposed

instability. Two had an emergency room thoracotomy for unrecordable blood pressure. Both subsequently died in the operating room. Another patient had an associated gunshot wound of the liver and died at operation.

Access to the vertebral artery at levels C_1–C_6 often required extensive dissection and osteotomy of the anterior rim of the transverse process of several vertebrae. Exposure was achieved via an incision along the anterior border of the sternomastoid muscle. The carotid sheath was identified and retracted anteriorly. The longus colli muscle, which lies between the body of the vertebra and the anterior tubercle of the transverse process, was swept medially off the bone with an osteotome. The anterior rim of the vertebral foramen (costotransverse bar) was then removed with bone rongeurs, and the artery was exposed and ligated (*Fig. 4*). The vertebral venous plexus within the canal may be the source of persisting bleeding and may need packing with an haemostatic agent. Blind clipping or transfixion of the vertebral artery through the intertransverse ligament is difficult and may damage the anterior nerve root, which lies just behind the vertebral artery[1,2]. This approach is technically difficult, but trauma surgeons should be familiar with it, because it may be necessary to ligate the vertebral artery in patients with severe bleeding or in those in whom radiological procedures fail. Other less demanding methods such as plugging the wound with haemostatic agents are not usually effective.

Results

There were four deaths, giving an overall mortality rate of 18 per cent. Three patients had major associated injuries. Only one patient with an isolated vertebral artery injury died. He had a cardiac arrest and a thoracotomy was performed in the emergency department (*Table 2*). No patient developed ischaemic neurological symptoms related to the vertebral artery injury, even two with bilateral vertebral artery injuries and one with ipsilateral vertebral artery and common carotid thrombosis.

Conservative management was successful in 13 patients. Embolization successfully controlled vertebral artery haemorrhage in two patients. It failed to control complex injuries to the vertebral artery with combined false aneurysm and AVF in three; subsequent suboccipital craniectomy for distal ligation was required in these patients.

Table 2 Characteristics of four patients who died

Patient no.	Injuries	Procedure	Comments
1	Vertebral artery	ERT	Died in operating room
2	Vertebral artery, internal jugular vein	ERT	Died in operating room
3	Vertebral artery, gunshot wound to the head	Observation	Died 3 days later
4	Vertebral artery, paraplegia, gunshot wound to the liver	Operation	Died in operating room

ERT, emergency room thoracotomy

Discussion

There are two reasons why there has been a considerable increase in the number of vertebral artery injuries recognized. First, an increased number of penetrating neck injuries, especially gunshot wounds, is seen in urban trauma centres. Second, angiography is now commonly used in the assessment of these injuries. Meier *et al.*[3] reported that the incidence of vertebral artery injuries increased from 3 per cent to 19 per cent of all cervical vascular injuries, after introduction of a policy of routine angiography. In a prospective study of 335 patients with penetrating neck injuries where angiography was not routinely performed, an overall incidence of vertebral artery injuries of 1·2 per cent, or 10 per cent of all major vascular injuries in the neck, was reported[4]. In another retrospective study of 271 patients, injuries to the vertebral artery constituted 10 per cent of all vascular neck injuries[1]. In an ongoing prospective study using routine angiography, the present authors have diagnosed vertebral artery injuries in eight of 147 patients (5 per cent), 29 per cent of all vascular injuries to the neck. This incidence was higher in patients with gunshot wounds (8·9 per cent) compared with knife injuries (5 per cent). Some vertebral artery injuries in asymptomatic patients or those with soft symptoms will be missed without routine angiography. In the present series four of the 13 patients with isolated vertebral artery injuries were asymptomatic and the lesion would have been missed without angiography. However, none of the asymptomatic patients required active treatment. This is consistent with previous studies which demonstrated that clinically occult, radiologically detected, minimal vascular injuries can safely be managed without operation[5].

Some patients with vertebral artery injury will require emergency surgery for control of active haemorrhage. The surgical approach to the injured vertebral artery in these patients can be a major technical challenge even for the experienced surgeon.

With the advance of interventional radiology, embolization has been effective in many vertebral artery injuries and is the procedure of choice in haemodynamically stable patients[6]. It should be considered in all patients undergoing diagnostic angiography. Proximal and distal embolization of the vertebral artery lesion is usually necessary to control active bleeding, false aneurysm or AVF. Antegrade distal embolization might not always be technically possible. Depending on the anatomy of the vertebrobasilar system, a retrograde approach from the opposite vertebral artery may be possible[7]. In three patients in this series the technique was not successful and suboccipital craniectomy was required to ligate the vertebral artery distally.

Non-operative management has a role in treatment of occlusive or minimal vertebral artery injuries[8,9]. In the present study all 13 patients with such an injury were successfully managed conservatively. Reid and Weigelt[10] believe that direct surgical intervention with proximal and distal ligation should be the procedure of choice. They state that arteriography is satisfactory for localizing the site of injury but may be inaccurate in characterizing the true extent of the vascular lesion. Vessels that were shown to be occluded on angiography were often found to be disrupted at surgical exploration. Despite this concern, and the possibility that some of these lesions may progress to false aneurysms or AVFs if left untreated, routine operation would subject most patients to an unnecessary, difficult and hazardous procedure. If a late complication occurs, it can be managed by embolization or, in occasional cases, additional surgery. It is likely that the increasing expertise of interventional neuroradiologists and newer catheter techniques will improve the success rates of embolization. Higashida *et al.*[6] successfully treated 21 traumatic vertebral artery fistulas with embolization. In the present series embolization alone failed to control or obliterate the vertebral artery lesions in three patients and surgical ligation of the distal vertebral artery artery was required.

In summary, occlusive or minimal vertebral artery injuries can safely be managed conservatively. Most other injuries to the vertebral artery may be treated with angiographic embolization. Surgical intervention should be reserved for patients with severe active bleeding or when embolization is not successful.

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Surgical workshop

Open diagnostic peritoneal lavage

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Diagnostic peritoneal lavage (DPL) plays an important part in the assessment of patients with blunt abdominal trauma. For reasons of safety the open technique is recommended by the Advanced Trauma Life Support (ATLS) Course for Physicians[1]. In the absence of good lighting and with limited assistance in the trauma suite this method can be time-consuming and often contaminated with blood especially in the obese patient. For similar reasons of safety open techniques for insertion of laparoscopic ports have been developed. The open technique for port insertion[2] provides a quick, virtually blood-free access to the peritoneum whatever the ambient conditions and equipment available. This technique is described below.

Surgical technique

The abdomen is prepared from xiphisternum to symphisis pubis with particular reference to the umbilicus. The umbilicus and surrounding skin are infiltrated with 1 per cent lignocaine 10 ml with adrenaline. The umbilicus is then everted using a toothed grasping forceps or towel clip. A small vertical incision is made from the apex of the umbilicus caudally. This reveals the umbilical tube which connects the skin to the peritoneum. The umbilical tube runs from the umbilical pit to the defect in the linea alba. This tube is incised and further blunt dissection through this plane gives access to the peritoneum (*Fig. 1*). The DPL catheter can then be inserted under direct vision and directed towards the pelvis. DPL is carried out according to ATLS guidelines. The fascial defect is simply closed at the end of the procedure using a single absorbable suture.

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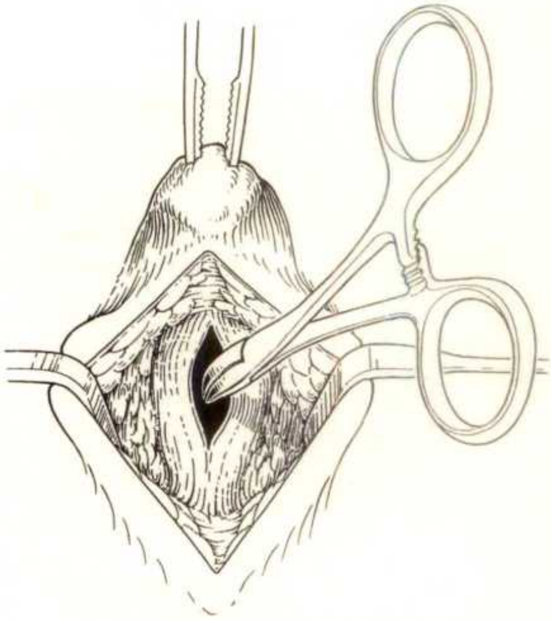

Fig. 1 The 'umbilical tube' is incised, and blunt dissection with artery forceps allows entry into the underlying peritoneal cavity

Acknowledgements

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Diaphragmatic herniation after penetrating trauma

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A study was made of 45 patients with diaphragmatic herniation after penetrating trauma. In 29 the diagnosis was established during the first admission (early presentation) and in 16 during a subsequent admission (delayed presentation). The mortality rate in the early presentation group was 3 per cent compared with 25 per cent in the delayed presentation group. The presence of gangrenous or perforated abdominal viscus in the chest cavity was the single most common and severe aggravating factor. The need for diagnosis of diaphragmatic herniation during the initial admission is emphasized. As isolated diaphragmatic injuries provide few helpful clinical features to aid diagnosis, appropriate investigations and good follow-up are of paramount importance in preventing late herniation of intra-abdominal viscera through a penetrating diaphragmatic injury.

Over the past 5 years there has been an enormous increase in civilian violence in South Africa especially that involving firearms, many of which are of high velocity. This is witnessed by the admission to this hospital of some 2500 patients with gunshot injuries and 700 with stab wounds to the trunk in 1992 alone. The authors' experience in the management of penetrating injuries to the diaphragm over a 3·5-year period was reported in 1988[1]. Diaphragmatic herniation was found in 24 cases; 14 of these were diagnosed during the first admission and the remaining ten during a subsequent admission. The mortality rate was 7·1 per cent in the former and 30 per cent in the latter group.

Diaphragmatic herniation after penetrating trauma is a relatively uncommon condition and the number of cases reported in each study is relatively small. It was therefore felt appropriate to re-evaluate the authors' experience over a longer period of time, particularly in view of the recent increase and changing patterns of trauma in this hospital.

Patients and methods

This is a retrospective study over a period of 7 years (August 1987 to July 1994). There were 45 patients with diaphragmatic herniation due to penetrating injury of the diaphragm. All except four were men. The mean age was 32 (range 23–48) years. Twenty-seven patients sustained knife wound and eighteen bullet injuries. In all patients with knife injuries the wound was located below the level of the nipples. In bullet injuries no relation was found between the site of the entrance wound and the presence of diaphragmatic injury. All 45 patients had injury to the left hemidiaphragm.

Follow-up of patients with penetrating chest trauma is extremely difficult. Only those with a complication returned to hospital. Some of the patients reported here presented late after being injured before the start of this study period. It is also conceivable that some patients injured during this period of study will re-present in the future with a diaphragmatic hernia.

Initial management and clinical presentation

During the period of the study all patients with a penetrating wound of the chest and evidence of pneumothorax, haemothorax or both, had an intercostal tube drain inserted in the fifth intercostal space at the mid-axillary line. Before insertion of the tube, finger palpation of the hemidiaphragm and lung was attempted in all patients. If this revealed a diaphragmatic defect, the patient underwent laparotomy after insertion of the tube. In all patients with penetrating wounds of the anterior abdomen, flank or back, the concept of selective conservatism was followed and patients were operated on on the basis of findings suggestive of haemorrhagic shock or peritonitis[2,3]. During the laparotomy, palpation of the diaphragm under direct vision was always performed. In 29 of the 45 patients the diagnosis of diaphragmatic herniation was made during the first admission (early presentation group) and in 16 it was made during a subsequent admission (delayed presentation group).

In the early presentation group, 18 patients were diagnosed as having diaphragmatic herniation immediately after admission (in the emergency room). Fourteen of these had a diagnostic chest radiograph. In six patients the herniating viscus was palpated during the process of insertion of the intercostal tube drain. There were four patients in whom the chest radiograph, although abnormal, was not suggestive of diaphragmatic herniation. In one of these four patients, the diagnosis was made on digital palpation of the herniating viscus through the tube thoracostomy incision, and in the remaining three it was made at exploratory laparotomy for intra-abdominal injury. Another three patients underwent laparotomy with the preoperative diagnosis of concomitant traumatic diaphragmatic hernia and injury of an intra-abdominal organ. Of the six patients who had an exploratory laparotomy, two had sustained stab wounds and four gunshot injury.

In 11 patients the diagnosis was made within 72 h of admission in the surgical ward. In ten of these, it was suspected or made on the basis of further chest radiographs performed for unsatisfactory clinical progress or routinely after intercostal tube-drain removal. In seven of the 11 patients in whom the diagnosis was made within 72 h of admission, additional radiological studies were required to confirm the diagnosis. These consisted of ultrasonography in three patients, computed tomography (CT) in two and barium meal in two. In one patient the diagnosis was established 48 h after admission when he developed diffuse abdominal pain and respiratory distress. The ward chest radiograph showed bowel above the left hemidiaphragm and the abdominal radiograph showed acute intestinal obstruction. The emergency room chest radiographs of all 11 patients were reviewed. In nine there was no radiological evidence of diaphragmatic hernia, although the films were abnormal (haemothorax, consolidation, obscured diaphragmatic shadows). In the remaining two, review of the initial films confirmed the presence of a small diaphragmatic hernia at the left costophrenic angle that had been overlooked. Therefore, the diagnostic accuracy of the emergency room chest radiograph in patients

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with hollow viscus in the chest was 55 per cent (16 of 29 patients).

In the delayed presentation group, there were 16 patients with a delay in diagnosis ranging from 5 months to 9 years (median 27 months) after the causative trauma. All 16 patients had an intercostal tube drain placed for penetrating chest injury during the original admission and three had undergone an exploratory laparotomy for simultaneous intra-abdominal trauma. The condition of the diaphragm was recorded as normal in one of them and not recorded in the other two. The chest films or the radiological reports of the original admission could be traced in seven patients. In none of these were the initial films diagnostic of diaphragmatic injury, although all were abnormal (e.g. haemothorax, pneumothorax, obscured diaphragmatic shadows). In four of the 16 patients the diagnosis of traumatic diaphragmatic hernia was made on chest radiographs taken as part of diagnostic work-up for other conditions. In two of these four, the stomach was shown to be the herniating viscus after insertion of a nasogastric tube and in the other two colonic herniation was shown by barium enema.

The remaining 12 patients presented with acute symptoms, the mean time between the beginning of symptoms and admission to hospital being 48 h (5 h to 4 days). Ten patients presented with severe upper abdominal pain, four with cardiorespiratory distress, six with a clinical picture of gastric or intestinal obstruction and three with an acute abdomen. Two patients were in septic shock. The chest radiograph was diagnostic or suggestive of diaphragmatic hernia in 11 of 12 patients. In the 12 patients who presented with an acute clinical picture, chest radiography was diagnostic in four, and ultrasonography or CT of the hemidiaphragm were required to establish the diagnosis in three and four patients respectively. In one patient, who presented with severe upper abdominal pain and a suspicious chest radiograph, laparoscopy was required to establish the diagnosis. Laparoscopic surgery was instituted in this department in 1991. On 20 occasions a laparoscopy has been performed either for the diagnosis of an injured diaphragm after a low penetrating chest injury or to rule out the presence of a hernia suggested by an abnormal chest radiograph. It was possible to diagnose one patient with a simple diaphragmatic injury and one with diaphragmatic hernia already mentioned.

Operative findings and management

The diaphragmatic defects identified at operation ranged from 1·5 to 7 cm in length. The organs herniated were colon in 23 patients, omentum in 21, small bowel in seven, stomach in seven and spleen in four. Multiple organs were herniated in six patients with early presentation and nine with delayed presentation. Gangrene or perforation of a hollow viscus was present in seven patients, one with early and six with late presentation. In all patients with early presentation, a laparotomy was sufficient for the reduction of the hernia and repair of the diaphragm. In the patients with delayed presentation, nine required a simultaneous anterolateral thoracotomy and laparotomy and seven had a thoracotomy or laparotomy alone.

The diaphragmatic defect was repaired with interrupted stitches of non-absorbable material.

Results

There were six postoperative deaths. The mechanism of injury, clinical presentation, operative findings and management, and cause of death of these patients are described in *Table 1*. Two patients in the acute presentation group died, one from septic complications of concomitant abdominal trauma. Thus only one of the 29 patients in this group died from diaphragmatic hernia, giving a mortality rate of 3 per cent. In this patient a gangrenous splenic flexure had to be resected. Four patients (25 per cent) in the delayed, obstructed presentation group died as a direct consequence of the diaphragmatic hernia. In all four patients the herniating viscus was found to be gangrenous.

There were ten significant postoperative complications among the 27 survivors in the early presentation group. Six developed pulmonary complications, one wound infection with abdominal dehiscence, one deep venous thrombosis and two intra-abdominal septic complications secondary to concomitant abdominal trauma. Of the 12

Table 1 Deaths in patients with penetrating diaphragmatic herniation

Patient no.	Age (years)	Early/late presentation	Interval from injury	Mechanism of injury	Clinical presentation	Herniating viscus	Operation	Cause of death
1	27	Early	4 h	Gunshot: left chest, abdomen	Acute abdomen, respiratory failure	Transverse colon (viable)	Laparotomy; colon reduced	Concomitant abdominal trauma and respiratory failure
2	43	Early	72 h	Stab: left posterior chest	Diffuse abdominal pain, respiratory distress	Splenic flexure (gangrenous)	Laparotomy; resection of splenic flexure and end colostomy	Respiratory failure
3	35	Delayed	7 months	Stab: left chest mid-axillary line	Diffuse abdominal pain and vomiting for 4 days before admission	Stomach and spleen (gastric gangrenous perforation)	Laparotomy and anterolateral thoracotomy, debridement gastrorraphy	Sepsis
4	37	Delayed	17 months	Gunshot: left chest	Left upper quadrant pain and episodes of haematemesis for 2 days before admission	Stomach (most of proximal stomach gangrenous)	Laparotomy and anterolateral thoracotomy, proximal gastrectomy	Respiratory failure
5	29	Delayed	3 years and 2 months	Gunshot: left chest	Severe upper and mid-abdominal pain. Clinical picture of bowel obstruction for 12 h before admission	Transverse colon (gangrenous, perforated)	Laparotomy and anterolateral thoracotomy; colonic resection and end colostomy	Sepsis, respiratory failure
6	43	Delayed	5 years and 8 months	Gunshot: left chest, abdomen	Several months history of episodes of abdominal pain and vomiting. Acute bowel obstruction and respiratory distress on admission	Transverse colon (gangrenous)	Laparotomy; colonic resection and end colostomy	Sepsis, respiratory failure

survivors of the late presentation group, six developed significant postoperative pulmonary complications; all six had presented with an acute clinical picture.

The mean hospital stay was 9 days for the early presentation and 19 for the delayed presentation group.

Discussion

Injuries of the diaphragm often challenge the surgeon by subtle presentation in the face of other more obvious injuries. Lack of reliable diagnostic methods and potential life-threatening sequelae of untreated patients compound the problem[4].

Either thoracic or abdominal penetrating trauma may lead to injury of the diaphragm. The dramatic increase of violent crime in this society means that diaphragmatic injuries will be encountered more frequently in civilian surgical practice. Such injuries have posed difficult diagnostic problems for the clinician, particularly when early symptoms or clinical findings suggestive of diaphragmatic injuries or actual herniation are lacking. Although many traumatic diaphragmatic hernias are immediately evident, there may be a long latent period before symptoms develop[5].

Many classifications exist of the natural history of diaphragmatic injuries. One particularly appropriate system described by Grimes[6] divides the presentation into three phases. An acute phase extends from the time of the original trauma to the apparent recovery from primary injuries. The latent phase then begins as intra-abdominal viscera occupy the defect and herniate into the thoracic cavity. This phase continues as long as the herniated viscera occupy a relatively benign position. The obstructive phase then begins with the signs of visceral obstruction or ischaemia as in any other case of hernia.

There has been no documentation of spontaneous closure of an injury to the diaphragm regardless of size. In fact, many authors[4,7–9] consider the small laceration to be more hazardous and associated with a higher incidence of strangulation.

Johnson[10], in his collective review of diaphragmatic trauma, emphasizes that at operation for penetrating injuries of the abdomen and chest a thorough inspection of the diaphragmatic surface should be made. In this way, most lacerations of the diaphragm will be detected. Many of these lacerations are not complicated by herniation and are easily missed unless specifically sought[10].

When the clinical findings suggest a diaphragmatic hernia and the chest radiograph is either normal or equivocal, ultrasonography[11] and CT[12] should be performed. Appropriate contrast gastrointestinal studies are also useful in the diagnosis of suspected diaphragmatic hernia, unless there is evidence of a perforated viscus. In this study the diagnosis of diaphragmatic hernia was achieved in six patients by ultrasonography, in six by CT, in two by barium meal and in one by laparoscopy.

Recently, Ivatury *et al.*[13] reviewed laparoscopic evaluation of the intrathoracic abdomen after penetrating injury and reported that the incidence of diaphragmatic lesions discovered by laparoscopy was similar to that reported after a mandatory laparotomy for thoracoabdominal wounds. They concluded that laparoscopy is an excellent modality for evaluation of the diaphragm. The present authors have had limited experience with the laparoscopic evaluation of patients with a suspected acute diaphragmatic injury (with or without herniation); in a series of 20 laparoscopies it was possible to diagnose a simple diaphragmatic injury in one patient and an acute hernia in another (included in the series). For logistic reasons routine laparoscopy is not being performed at present and the authors are unsure about the value of this investigation for the prevention or diagnosis of diaphragmatic hernia.

Thoracoscopy has been used to identify diaphragmatic injury in the past, but has not been widely accepted because of limitations of equipment and experience[14]. A preliminary experience in diagnosing diaphragmatic injury by videothoracoscopy has produced encouraging results[15]. Induction of pneumoperitoneum[16], instillation of contrast or radioactive material into the pleural or peritoneal cavities[16–18] and peritoneal lavage[19–20] to detect diaphragmatic injuries are alternative techniques of which the authors have no experience.

This relatively extensive experience of 45 cases with penetrating diaphragmatic herniation confirmed the good prognosis of early presentation and the bad prognosis of delayed obstructed presentation as reported earlier from this hospital[1]. The mortality rate was no different in these two reports. The presence of gangrenous or perforated viscus was the one most severe aggravating factor as five of seven patients with this operative finding succumbed. There was only one death in the 38 patients without gangrene or perforation.

The need for diagnosis of diaphragmatic herniation after penetrating injury during the initial admission (early acute presentation) or early during a subsequent admission (delayed obstructive presentation) cannot be overemphasized. Also, as isolated diaphragmatic injuries provide few helpful clinical features to aid the diagnosis, appropriate investigations and good follow-up are of paramount importance in preventing late herniation of intra-abdominal viscera through a penetrating diaphragmatic injury.

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Audit of outcome of major surgery in the elderly

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The clinical outcome of 152 patients aged 65 years or over who were referred to the author's institute between August 1990 and August 1991 with certain specified gastrointestinal malignancies and acute, life-threatening abdominal conditions, were audited concurrently. Two groups were considered: patients aged 65–79 years and those over 80 years. The mortality rate within 30 days of surgery was 14 per cent in both age groups, although significantly fewer patients aged over 80 years (35 of 54) were considered suitable for surgery than in the 65–79 years age group (84 of 98) ($0{\cdot}01 > P > 0{\cdot}001$). Morbidity after operation and cost of treatment were not significantly different between the two groups. Two years after surgery 40 per cent of the patients aged over 80 years and 58 per cent of those aged 65–79 years were alive. Quality of life in these survivors was good with 85 per cent of those aged over 80 years living at home and 72 per cent fit enough to undertake light work.

In England and Wales the elderly proportion of the population is gradually increasing. In 1981 14·6 per cent were over 65 years and 2·4 per cent over 80 years, while in 1991 16·1 per cent were over 65 years and 3·8 per cent over 80 years[1]. Evidence also suggests that the elderly are more likely to be admitted as surgical patients and those aged 65 or over have approximately three times the risk of being admitted as general surgical patients when compared with younger members of the population[2].

The postoperative mortality rate after major surgery is higher in the elderly, especially in those over 80 years of age[3–13], although much of this increased risk relates to the severity of the medical and surgical conditions from which the patients suffer[3,7,10,14–17]. Furthermore, elderly patients are more likely to present as emergencies[4,5,18–20] and this also confers increased risk[4,5,10,16,17,19–22]. If these factors are accounted for by careful selection and exclusion of 'non-viable' patients most authors consider that age alone does not greatly increase the postoperative mortality rate[7,9,14–17,23–25]. The importance of age as a risk factor for the development of postoperative complications is uncertain. Some have found an increased tendency to certain complications in the very elderly[4,6,26]. Others have observed no increased risk with age[24,27]. Overall, the results are inconsistent and, as with the mortality rate, the relationship is probably more to do with the underlying surgical and medical conditions than with age itself.

Information on the effect of increasing age on other aspects of care, such as costs of treatment and the long-term quality of life after major surgery, is also sketchy and inconclusive[6,12,26–29] in spite of the importance of these issues in modern medical practice.

Patients and methods

A concurrent audit was carried out on all patients aged 65 years or over who were referred to this department between 14 August 1990 and 13 August 1991 and who had one of the following diagnoses at the time the decision was made on definitive treatment: carcinoma of the oesophagus, stomach, colon or rectum; ruptured abdominal aortic aneurysm; acute generalized peritonitis, intestinal obstruction, upper gastrointestinal haemorrhage or strangulated external hernia.

All patients with these diagnoses were included in the study if the most senior surgeon considered that, if the patient was otherwise medically fit, then surgery was or would be essential, and without surgery the patient would almost certainly die as a result of the surgical pathology.

Patients were divided into two groups, those aged 65–79 years and those over 80 years for the purpose of assessing and comparing clinical outcome. Medical data were collected concurrently by an audit assistant using a prepared proforma. Subsequent audit of early outcome was carried out by peer review of deaths and complications at monthly surgical audit meetings.

Assessment of quality of life was undertaken using a questionnaire completed by the audit assistant after visiting the patient, telephone enquiry or from progress notes, and was undertaken at the time of discharge (or decision not to operate) and then at 3, 6, 12 and 24 months.

Estimation of the cost of each treatment episode was based upon local figures of £200 per day for inpatient stay and £400 per hour of operating theatre time.

Statistical analysis was undertaken using the χ^2 test (discrete variables), Student's t test (for parametric non-discrete variables), and on non-parametric results using the Mann–Whitney U test.

Distribution of surgical conditions in the 152 patients studied is given in *Table 1*. Of the 98 patients aged 65–79 years the mean age was 73·1 years, male : female ratio was 1·45 : 1 and 61 (62 per cent) were admitted electively, 35 (36 per cent) as emergencies

Table 1 Patients and diagnoses

	65–79 years		Over 80 years	
	Number	Number operated	Number	Number operated
Carcinoma of the oesophagus	4	3	4	2
Carcinoma of the stomach	8	5	2	2
Carcinoma of the colon and rectum	54	51	15	11
Ruptured AAA	9	5	4	2
Acute generalized peritonitis	2	2	14	7
Acute intestinal obstruction	11	9	12	10
Major upper gastrointestinal haemorrhage	2	2	0	0
Acute strangulated external hernia	8	7	3	1
Total	98	84	54	35

AAA, abdominal aortic aneurysm

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and two (2 per cent) were not admitted. Of the 54 patients aged over 80 years the mean age was 84·5 years, male:female ratio was 0·93:1 and only 16 (30 per cent) were admitted electively, 35 (65 per cent) as emergencies and three (6 per cent) were not admitted.

All patients in the study were drawn from a resident population of the district of 129 800 which approximately doubled during the summer season. Treatment was undertaken by two consultant general surgeons during the 7·5-month period from 14 August 1990 to 31 March 1991, and by three consultant general surgeons from 1 April 1991 to 13 August 1991. These consultants were supported by one associate specialist and two registrars. Of the 119 patients who underwent surgery 71 (60 per cent) presented electively; initial surgery was undertaken by a consultant in 41 of these patients (58 per cent), the associate specialist in 17 (24 per cent) and a registrar in 13 (18 per cent). Some 48 patients presented as emergencies and initial surgery was undertaken by a consultant in 17 of these (35 per cent), the associate specialist in 10 (21 per cent) and a registrar in 21 (44 per cent).

Decisions on whether patients underwent surgery (*Table 1*) and the extent of that surgery were based on clinical assessment of fitness for surgery (after consultation with the anaesthetist), known extent of the lesion and, where indicated, quality of life (after discussion with the relatives). It was the view of all three consultants that the patient's age should have only a minor influence on these decisions. Of the 87 patients who presented with malignant neoplasms, in the group aged between 65 and 79 years 47 patients (80 per cent) underwent excision which was thought to be curative at the time of surgery while 12 (20 per cent) underwent surgery which was considered palliative. In those aged over 80 years nine patients (60 per cent) underwent surgery which was considered curative while six (40 per cent) underwent surgery considered palliative. The surgical procedures which were undertaken on patients who presented with ruptured abdominal aortic aneurysm, acute generalized peritonitis and acute intestinal obstruction are given in *Table 2*.

Table 2 Primary surgical procedures performed for acute abdomen

	65–79 years	Over 80 years
Ruptured abdominal aortic aneurysm	5	2
Resection and straight graft	5	1
Resection and bifurcated graft	0	1
Acute intestinal obstruction	9	10
Division of adhesions	4	3
Division of adhesions and small bowel resection	1	3
Colectomy	2	2
Colectomy and defunctioning colostomy	1	0
Defunctioning colostomy	1	2
Acute generalized peritonitis	2	7
Oversewing perforated duodenal ulcer	0	2
Appendicectomy	1	1
Colectomy (for ischaemia)	0	1
Defunctioning colostomy	1	1
Hartmann's operation	0	2

Results

Early outcome

Mortality within 30 days. *Table 3* shows the distribution of deaths in relation to age and admission method. *Table 4* correlates deaths after surgery with possible risk factors. Although there were differences between the pathology and therefore the surgery undertaken in the different groups, the data suggest that age alone did not increase postoperative mortality rate. However, the mortality rate of all admissions, both operated and unoperated, was higher in those aged over 80 years (33 per cent) than in those aged 65–79 years (20 per cent) as significantly more patients in the older age group were considered unfit for surgery ($0{\cdot}01 > P > 0{\cdot}001$). Similarly, emergency surgery did not itself confer a significantly higher mortality rate but emergency admission did, with 36 per cent of all emergency admissions dying compared with 14 per cent of elective admissions ($0{\cdot}01 > P > 0{\cdot}001$). The postoperative mortality rate was significantly increased in patients with an acute respiratory history and in those with dyspnoea on minimal exertion. However, these variables were not independent and three of the four patients with an acute respiratory history also had dyspnoea on minimal exertion. Nevertheless, when these patients with an acute respiratory history were excluded, dyspnoea on minimal exertion alone was associated with a significant increase in postoperative mortality rate from 9 to 31 per cent ($0{\cdot}05 > P > 0{\cdot}02$). The preoperative American Society of Anesthesiologists (ASA) grade[30] gave some indication of operative risk: patients with grades I and II had a better chance of survival than those with grades III and IV ($P < 0{\cdot}001$). Nevertheless, no ASA grade or risk factor was identified in which there was no chance of survival.

When the 17 patients who died after surgery were submitted to audit by peer review analysis four were considered 'inevitable' (three inoperable carcinoma, one inoperable aortic aneurysm) and 10 were 'acceptable' risks considering the major surgery required. For three patients who died after operation (all over 80 years) specific points of potential improvement in care were identified. In two patients there was inaccuracy in the preoperative diagnosis of emergency patients, in one patient leading to delay before surgery for acute abdomen and in the other leading to an unnecessary operation in a patient with

Table 3 Mortality rate within 30 days by age and admission method

	65–79 years				Over 80 years			
	n	Number operated	Operated mortality rate	Non-operated mortality rate	*n*	Number operated	Operated mortality rate	Non-operated mortality rate
Elective	61	57	5 (9)	2 (50)	16	14	2 (14)	2 (100)
Emergency	35	27	7 (26)	5 (62)	35	21	3 (14)	10 (71)
Not admitted	2	0	—	2 (100)	3	0	—	2 (67)
Total	98	84	12 (14)	9 (64)	54	35	5 (14)	14 (74)

Values in parentheses are percentages

Table 4 Effect of risk factors on postoperative mortality rate at 30 days (operated patients only)

Risk factor	Number of patients in whom risk factor was recorded as: Present	Absent	Mortality rate when risk factor is: Present	Absent	Increase in mortality rate with risk factor	P
Age over 80 years (*versus* 65–79 years)	35	84	14*	14*	0	n.s.
Emergency admission	48	71	21*	10*	+11*	n.s.
Acute respiratory history	4	113	75*	12*	+63*	$0{\cdot}01>P>0{\cdot}001$
Chronic respiratory history	14	103	21*	14*	+ 8*	n.s.
Dyspnoea on minimal exertion	19	98	37*	10*	+27*	$0{\cdot}01>P>0{\cdot}001$
Smoker	20	97	15*	14*	+ 1*	n.s.
Incision adjacent to diaphragm	47	70	17*	13*	+ 4*	n.s.
History of myocardial infarction	6	111	17*	14*	+ 2*	n.s.
History of angina	7	110	14*	14*	0*	n.s.
History of hypertension	30	87	20*	13*	+ 7*	n.s.
History of diabetes	9	108	22*	14*	+ 8*	n.s.
ASA grade I	49		12*			$P<0{\cdot}001$
II	41		5*			
III	23		30*			
IV	3		67*			
V	0		—			

*Values are percentages. ASA, American Society of Anesthesiologists; n.s., not significant

acute pancreatitis. In the third patient surgery was thought to be too extensive after consideration of the patient's age and pathology.

Examination of the 33 patients who were refused surgery revealed a 30-day mortality rate of 23 (70 per cent). Of these, four were considered 'inevitable' (terminal care) and 17 'acceptable' (unfit for surgery). Two patients (both aged between 65 and 79 years) suffered from ruptured abdominal aortic aneurysm which was not diagnosed before death although it is doubtful whether this affected survival.

Ten patients were refused surgery but survived for more than 30 days. Of these, eight had a malignancy and all died within 7 months. One patient aged 86 years recovered from acute intestinal obstruction but died 8 months later from bronchopneumonia, and one 71-year-old patient recovered from a strangulated incisional hernia but died 1 year later from cardiac failure.

Postoperative complications. Complications in the two groups of patients were submitted to peer review analysis. A complication was considered 'avoidable' if there was evidence that it did not predate the surgery and was not an expected consequence of the patient's presenting condition. A complication was considered 'unacceptable' if the probable cause was thought to be faulty technique.

The wound infection rate of 12 (10 per cent) of 119 patients was considered 'acceptable' for the type of surgery, although one infection in a clean case (incarcerated incisional hernia) was considered 'unacceptable'. This was from a total of 24 clean cases in the series.

Wound dehiscence occurred in two patients. One was secondary to an anastomotic leak but in the other no cause was found and this was considered faulty technique and thus 'unacceptable'.

Anastomotic leakage occurred in four patients, all in the 65–79-year-old group. There were two radiological leaks following gastro-oesophagectomy for carcinoma from a total of four such procedures. All these anastomoses were stapled and the two leaks healed without major clinical problem. There were two major clinical leaks following (low) anterior resection. Neither patient had a defunctioning colostomy performed at the time of initial surgery and both required a second emergency operation; one died. These two leaks occurred from a total of 12 anterior resections, all of which were stapled and four were covered by a defunctioning colostomy. There were no leaks from the 70 other anastomoses which were mainly colonic, of which 58 were handsewn and 12 stapled.

Intra-abdominal abscess occurred in two patients, one secondary to an anastomotic leak ('avoidable' but 'acceptable') and the other secondary to perforated diverticulitis ('unavoidable').

Postoperative intestinal obstruction occurred in one patient following acute appendicectomy. This complication was considered 'unacceptable' as there had been delay in original diagnosis.

Postoperative urinary tract infection, based on clinical features and positive urine cultures, was found in 13 patients. Twelve of these had been catheterized and infection was considered to be secondary to this procedure. A total of 107 patients who underwent surgery in the study were catheterized. The urinary infection rate for those patients, at 12 of 107 (11 per cent), was considered to be too high.

Seven patients, all in the 65–79-year-old group, developed postoperative urinary retention, of whom four required prostatectomy. This complication was considered 'unavoidable'.

Postoperative chest infection (with positive sputum culture or radiological changes) occurred in 11 patients. In one there was a pre-existing acute respiratory infection; the remainder were considered 'acceptable' but 'avoidable'.

There was one clinically apparent deep venous thrombosis and one proven non-fatal pulmonary embolus. Both had received prophylactic subcutaneous heparin.

Two patients developed haematemesis after surgery.

Both were found on endoscopic examination to have duodenal ulcers and were successfully treated conservatively.

A pressure sore occurred in one patient. This was assessed as 'unacceptable'.

Anaemia (haemoglobin less than 100 g/l) occurred after surgery in seven patients. One patient was a Jehovah's Witness and two had unexpected postoperative haematemesis. These three were considered 'unavoidable'.

Postoperative electrolyte imbalance (serum electrolytes outside normal range) occurred in 15 patients, eight of whom had low Na^+, seven had low K^+ and five had high K^+. In one patient the electrolyte imbalance was not corrected before discharge and this was assessed as 'unacceptable'.

The appropriateness of treatment of the complications described above was also reviewed. With the exception of the one patient sent home with abnormal serum electrolytes all complications were considered to have been satisfactorily treated.

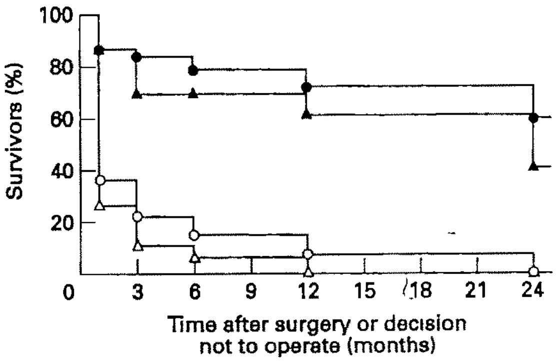
An unscheduled return to the operating theatre for complications developing after surgery (excluding prostatectomy for urinary retention) took place for four patients; two of these died. Two patients aged between 65 and 79 years were re-explored for major colorectal anastomotic leaks. Both had undergone elective stapled anastomosis which had been performed below the level of the peritoneal reflection without a covering colostomy. One patient was treated by defunctioning colostomy and drainage with subsequent good progress. In the other the anastomosis had completely disrupted. An end colostomy was fashioned with drainage of the pelvis but the patient died from septicaemia. One patient (aged 82 years) was successfully re-explored for bleeding which appeared to be coming from the upper anastomosis after resection of an abdominal aortic aneurysm; this patient survived. One patient (aged 83 years) required re-exploration for intestinal obstruction 8 days after undergoing acute appendicectomy. At the second operation there was an inflamed and knotted mass of terminal ileum in the right iliac fossa which required resection. The patient never fully recovered from this second operation, slowly deteriorated and died 22 days after surgery.

Resource implications. *Table 5* shows the length of stay during the initial (main) admission, duration of surgery (including all operations during this admission) and an estimated cost of initial treatment. Although this does not include any subsequent admissions, the readmission rates at 3 months after surgery were similar in the two groups (three of 35 aged over 80 years and seven of 84 in the 65–79 years group).

There was no significant difference in length of stay between the two age groups.

Mean duration of surgery was significantly longer in the 84 patients aged 65–79 years who underwent surgery than the 35 patients aged over 80 years ($0{\cdot}01 > P > 0{\cdot}001$) with similar results in the 72 patients who survived operation aged 65–79 years compared with the 30 survivors aged over 80 years ($0{\cdot}01 > P > 0{\cdot}001$). Duration of surgery in those who died was not significantly different.

Estimated cost of treatment was not significantly different between the two age groups in terms of cost per treatment episode. In both groups the cost of treatment was highest in those who survived operation.



No. at risk	0	3	6	12	24
Operated 65–79 years	84	70	65	60	49
Operated over 80 years	35	24	24	21	14
Not operated 65–79 years	14	3	2	1	0
Not operated over 80 years	19	2	1	0	0

Fig. 1 Crude survival after surgery in patients aged 65–79 years (●) and those over 80 years (▲), and survival in those who did not undergo surgery aged 65–79 years (○) and over 80 years (△)

Table 5 Length of stay during initial (main) admission, duration of surgery during this admission and estimated cost of initial treatment

	n	Length of stay in hospital (days)	Duration of surgery (min)	Estimated cost of of initial treatment (£)
65–79 years				
All patients	98	16	111	3840
All operated patients	84	17	131*	4210
Operated survivors	72	18	133*	4460
Operated deaths	12	10	118	2760
Non-operated patients	14	8	—	1680
Over 80 years				
All patients	54	16	63	3620
All operated patients	35	20	97*	4580
Operated survivors	30	21	98*	4830
Operated deaths	5	13	88	3110
Non-operated patients	19	8	—	1560

Values are mean unless otherwise stated. *Differences between age groups were significant

Table 6 Changes in mobility and levels of dependency after major surgery in patients who survived 2 years

	65–79 years old ($n = 49$)			Over 80 years old ($n = 14$)		
	Before surgery	At 1 year	At 2 years	Before surgery	At 1 year	At 2 years
Fully mobile	76	63	61	57	43	29
Some limitation but able to do light work	23	31	26	29	36	43
Mobility severely limited but able to get about independently	2	6	12	7	14	21
Disabled; dependent or chair bound	0	0	0	7	7	7
Fully independent	94	92	88	79	71	64
Able to live at home	6	4	6	21	14	21
Totally dependent/in nursing home	0	4	6	0	14	14

Values are percentages

Late outcome

Mortality. *Fig. 1* gives crude survival rates 2 years after initial admission/operation. For patients who underwent surgery and survived to 2 years *Table 6* shows how levels of mobility and dependency were altered.

Subjective satisfaction was also recorded at 2 years in those who survived operation. Of the 49 patients aged 65–79 years, 44 considered the outcome of operation to be 'excellent' or 'very good', three had some symptoms and considered it 'satisfactory' while two regarded the outcome as 'unsatisfactory' (one because of an incisional hernia and the other because of local recurrence of carcinoma of the colon). Of the 14 aged over 80 years, 13 considered the outcome 'excellent' or 'very good' while one considered the outcome only 'satisfactory' (because of diarrhoea after subtotal colectomy).

Discussion

A progressive rise in the number of elderly and very elderly people in the UK, together with a greater chance of these people requiring admission as surgical patients, has resulted in a marked increase in the number of surgical treatment episodes in these groups[1,2]. Previous studies have shown a longer inpatient stay for such elderly patients after major surgery[6,10,31]. However, in the present study of a mixed group of life-threatening surgical conditions very elderly patients (over 80 years) were less likely to undergo surgery after being admitted, and those who did undergo surgery had shorter operations. Hence, although the number of surgical treatment episodes in the very elderly is progressively rising, there is no good evidence that each treatment episode is any more costly than in younger patients.

The reasons for shorter duration of surgery in the very elderly were multifactorial and included the judgement of the surgeons and anaesthetists at the time as to what was appropriate for each patient. However, it was also noted that 65 per cent of those over 80 years were admitted as emergencies compared with 36 per cent of the 65–79 years group, and that the surgery required for emergency conditions was often relatively quick (*Table 2*) compared with that for elective operations, which in this series were all for neoplastic conditions. Furthermore, of the patients who underwent surgery for malignant neoplasms more of those aged 65–79 years (80 per cent) underwent 'curative' excision than did the patients over 80 years (60 per cent).

In the present study there was no difference in early postoperative mortality rate (at 30 days) between the two groups and no evidence of any increased risk of postoperative complications in the very elderly. However, the mortality rate of all admissions, both operated and non-operated, was higher in the group over 80 years old (33 per cent) than in the 65–79 years group (20 per cent), and in emergency cases (36 per cent) than in elective cases (14 per cent). This suggests that very elderly and emergency patients with life-threatening surgical conditions are more likely to die than younger or elective patients because their medical condition on admission is considered to make them less likely to survive surgery and not because the surgery itself carries a significantly greater risk. Furthermore, the audit of deaths and complications in this series of patients identified inaccuracy in the preoperative diagnosis of emergency admissions as the most common cause of 'avoidable' death. Of the 17 deaths after surgery better preoperative diagnosis may have enabled one patient to have been treated earlier, one to have avoided surgery for acute pancreatitis and four inoperable patients to have avoided unnecessary surgery. Of 23 deaths in patients who did not have operations, potentially curable conditions were identified at post-mortem examination in two emergency cases. It may be that the conclusion of the Report of the National Confidential Enquiry into Perioperative Deaths 1991/1992[32] that 'There is a need for more consultant involvement in the theatre, particularly for emergency cases' is less relevant than the need for more involvement in the preoperative diagnosis and medical management of these patients and possibly the greater use of diagnostic imaging in the emergency situation.

Two years after major surgery, 58 per cent of the 65–79 years group and 40 per cent of those over 80 years were still alive. Of these survivors the quality of life at 2 years, as measured in terms of dependency and mobility was, not surprisingly, better in the younger group. Nevertheless, even in those over 80 years of age 85 per cent were living at home with or without some help, 72 per cent were sufficiently mobile to undertake light work and 93 per cent considered the outcome of their surgery to be 'excellent' or 'very good'. As the alternative to surgery was almost certain death, these figures strongly support the view that necessary major surgery should not be withheld from the very elderly on the grounds of age alone.

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Cell kinetics *in vivo* of human breast cancer

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Rates of cell proliferation within tumours may provide prognostic information and help in the rational administration of chemotherapy and radiotherapy. *In vivo* labelling with 5-bromo-2'-deoxyuridine (BrdU) was used in 89 women with breast cancer to determine the labelling index for BrdU (BLI), the length of S phase (T_S) and the potential doubling time of the tumour (T_{pot}). Kinetic data were obtained in 84 patients. The median BLI was 3·2 per cent, T_S 12 h, and T_{pot} 12·5 days. There was no systematic difference in the labelling index determined by flow cytometry and by manual counting on sections. Labelling indices were significantly higher in aneuploid tumours, and in tumours not expressing oestrogen receptors, but were not correlated with tumour size, nodal status, or expression of c-*erbB2*. *In vivo* measurement of tumour cell kinetics can be made rapidly and reliably in the majority of human breast cancers, and may have a role to play in planning therapy.

Since abnormal growth is a defining characteristic of tumours, there has been a longstanding interest in measuring tumour growth. The rationale is threefold: knowledge of tumour growth characteristics might provide prognostic information; it might form a rational basis for the use of cell cycle dependent therapies such as radiotherapy and chemotherapy; and if progress is to be made, tools are required to study the biological mechanism of tumour cell growth. Measurement of the rate of growth of whole tumours is rarely possible by observation since few accessible tumours are left untreated for an adequate time for significant growth to occur. Moreover, in biological terms, the growth behaviour of the tumour cells (tumour cell kinetics) may be more relevant than the growth of the whole tumour mass.

The hypothesis has been that rapidly dividing tumours are more 'aggressive' in behaviour, and will carry a poorer prognosis. In human breast cancer, studies that determine the proportion of cells in the DNA synthetic (S) phase of the cell division cycle broadly agree with this concept. Such methods involve *in vitro* labelling of tumour explants with tritiated thymidine (measurement of the thymidine labelling index)[1], or the use of computer modelling to analyse flow cytometric histograms of the DNA content of populations of tumour nuclei (determination of the S phase fraction (SPF))[2]. Tumours with a high thymidine labelling index carry a worse prognosis than those with a low index[3–5]. Similarly, SPF above median has been reported to be an independent predictor of poor outcome[6]. The extent of the difference in survival between good and poor outcome groups as defined by median values of thymidine labelling index and SPF is of the order of 10–15 per cent after 5 years in univariate analysis; however, the authors' previous data indicate that the significance of these factors is reduced when multivariate analysis is undertaken[7,8].

Both thymidine labelling index and SPF are 'static' parameters of tumour cell kinetics which provide information about the cell cycle distribution at a point in time only. The rate of cell production within the tumour also depends on the rate at which cells complete the cell cycle. One way to obtain these data is by *in vivo* labelling with the thymidine analogue 5-bromo-2'-deoxyuridine (BrdU). The development of monoclonal antibodies capable of detecting BrdU in DNA[9] permits study without the use of radioisotopes. By allowing time between administration of the drug and tissue biopsy, combined with the use of multiparameter flow cytometry, mathematical methods have been developed for estimation not only of the distribution of cells within the cell cycle but also the rate of cycle transit and potential doubling time of the tumour (T_{pot}; the time that the tumour would take to double in volume in the absence of cell loss)[10,11]. This additional information may be of greater prognostic value, but may also provide more relevant information for the selective use of cell cycle related therapies. The application and validity of this method in cell culture systems and a variety of tumour types have been demonstrated[12,13].

One report has provided data on the results of BrdU labelling in a substantial number of human breast cancers[14]. The present study details the results obtained from the administration of BrdU to 89 women with early breast cancer, and includes a comparison of results obtained by flow cytometry with those from counting immunohistochemically stained sections, and an analysis of the relationship between expression of the oncogene c-*erbB2* and tumour cell kinetics.

Patients and methods

Some 89 postmenopausal patients who had excision of a breast cancer of more than 2 cm in diameter took part in this study after written, informed consent was obtained. Approval for the project was given by relevant ethics committees. The way in which the patient was treated formed no part of this study, and was entirely at the discretion of the surgeons involved. Patients having either breast conservation or mastectomy were included, as were those having adjuvant radiotherapy or chemotherapy.

Demographic data about each patient were obtained from hospital notes at the time of BrdU labelling; the pathological tumour size and degree of involvement of axillary nodes coded by the tumour node metastasis (TNM) classification, and the level of oestrogen receptors within the tumour using a dextran–charcoal method (with a cut-off of 20 fmol per mg protein) were recorded where available.

BrdU 200 mg (Takeda, Osaka, Japan, and latterly Cancer Research Campaign Formulation Unit, Department of Pharmacy, Strathclyde University, Glasgow, UK) was

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administered as an intravenous bolus 4–10 h before surgery. Samples of each tumour were taken from the fresh specimen and fixed in 70 per cent cold ethanol.

Determination of tumour cell kinetics

Staining for BrdU incorporation and DNA content was by an adaptation of the method described by Dolbeare *et al.*[15], similar to the Hedley method[2] for using paraffin-embedded material as a starting point for flow cytometric study of tumours. The rationale for embedding and deparaffinization of tumour samples was to utilize the minimum volume of tumour for each assay, and to provide contiguous material for histological examination and to establish reproducibility. A portion of each tumour sample was embedded in wax using standard histological techniques. A single 50-μm section was then cut, wrapped in 50-μm mesh, dewaxed and rehydrated through graded alcohols. The rehydrated section was disaggregated by incubation in 0·5 per cent pepsin (Sigma, Poole, UK), pH 1·5 at 37°C for 30 min, and the resultant suspension was cleared of large aggregates by passage through a 26-G hypodermic needle and then a 50-μm mesh. Following this, DNA was partially denatured by incubation of the nuclear suspension in hydrochloric acid 2 mol/l for 30 min. After washing in phosphate-buffered saline including 0·5 per cent bovine serum albumin (Sigma) and 0·05 per cent Tween (Sigma), BrdU was stained with a 1:30 dilution of mouse anti-BrdU (Dako, High Wycombe, UK) at room temperature for 1 h. The primary antibody was detected using a 1·40 dilution of fluorescein-labelled rabbit antimouse antibody (Dako) for 30 min. After further washing, total DNA was stained with propidium iodide at a final concentration of 10 μg/ml.

Specimens were run on an Epics Profile II flow cytometer (Coulter, Hialeah, Florida, USA). A peak *versus* total red fluorescence histogram was used to gate out any nuclear multiples, and a plot of red *versus* green fluorescence was then used to calculate the labelling index for BrdU (BLI), the length of S phase (T_S) and T_{pot} using the method of Begg *et al.*[10]. BLI was calculated differently in diploid and aneuploid tumours. In the latter case the population studied consisted of tumour cells only, whereas in the case of diploid tumours the tumour cells were mixed with non-tumour cells such as fibroblasts, lymphocytes and endothelial cells. To compare tumours of different ploidy, the total labelling index (TLI) was defined as the number of labelled cells within all populations, divided by the total number of cells in all populations.

T_S was not calculated from histograms in which the population of labelled undivided tumour cells was not distinct from other labelled cells. DNA content histograms derived by analysis of propidium iodide staining alone were used to estimate the SPF using a rectangular model of S phase[16], following exponential background subtraction. This analysis was performed using the Cytologics software package (Coulter).

Immunohistochemistry

Labelling indices from flow cytometric data were compared with manual counts of labelled nuclei on immunohistochemical preparations from 50 of these tumours. The methods used have been described previously[17]. Specimens for immunohistochemistry were immunostained for BrdU by an avidin-biotin complex method. Counting was performed on random fields selected with an 'England' field-finding stage graticule. Labelled and total tumour cell counts were recorded for every field, with the aid of a 10 × 10-square eyepiece graticule to a total of 2000 cells.

Sections of 4 μm from the alcohol-fixed, paraffin-embedded blocks used for kinetic studies were stained immunohistochemically to determine expression of c-*erbB2*, using the 21N antipeptide polyclonal antibody (a gift from Dr W. Gullick, Imperial Cancer Research Fund, London). Stained sections were assessed by two observers, and were regarded as positive for expression of c-*erbB2* if groups of membrane-stained tumour cells were present.

Results

Observed values of kinetic parameters

No specimen was obtained in two patients given BrdU, and in two other cases no invasive tumour was present in the specimen taken for kinetic studies. From the 85 remaining patients given BrdU, a labelling index was obtained in 84. Calculation of T_S was made in 67 of these 84 histograms (80 per cent).

The distribution of values for each of the four kinetic parameters is summarized in *Table 1*. *Fig. 1* demonstrates the relationship between BLI and T_S for each individual tumour; there was no evidence of correlation between the two. The two components of T_{pot} thus act as independent variables.

Relationship between kinetic parameters, tumour ploidy and S phase fraction

There was a significant difference in BLI and TLI between the ploidy groups, with aneuploid tumours showing higher labelling. This was more marked in respect of BLI (diploid median 1·2 per cent, aneuploid median 5·2 per cent; $W=905$, $P<0{\cdot}00005$, 95 per cent confidence interval (c.i.) for difference in medians 2·3–4·6 per cent, Mann–Whitney U test), which was predictable given the inherent bias in favour of aneuploid tumours in making this calculation. The TLI corrects for this effect, and the difference between the groups could be ascribed to the method of calculation (diploid median 1·3 per cent,

Table 1 Summary of cell kinetic parameters for all tumours

	n	
BLI (%)	84	3·2 (0·4–12·9)
TLI (%)	84	2·6 (0·5–8·4)
T_S (h)	67	12·0 (4·8–32·0)
T_{pot} (days)	67	12·5 (3·7–153)

Values are median (range). BLI, 5-bromo-2'-deoxyuridine labelling index; TLI, total labelling index; T_S, length of S phase; T_{pot}, potential doubling time

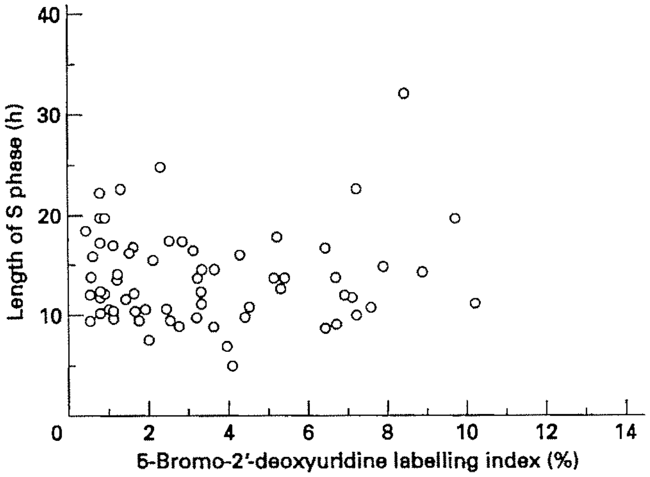

Fig. 1 5-Bromo-2'-deoxyuridine labelling index *versus* length of S phase for each of the 67 tumours for which both parameters could be measured. ($r_S = -0{\cdot}01$, $P = 0{\cdot}93$)

aneuploid median 3·3 per cent; $W=1111$, $P<0·0014$, 95 per cent c.i. for difference in medians 0·5–2·2 per cent). There was no difference in T_S between the groups (diploid median 11·7 h, aneuploid median 13·6 h; $W=1024$, $P=0·14$, 95 per cent c.i. for difference in median $-3·4$–0·6 h).

The SPF could be calculated for 74 histograms. Median SPF was 8·25 (range 0·8–39·8) per cent. Labelling indices for this subset of tumours were: BLI median 3·3 (range 0·4–12·2) per cent; TLI median 2·1 (range 0·5–8·3) per cent. The BLI and SPF for each individual tumour are plotted in *Fig. 2*. Correlation between the two was observed ($r_S=0·69$, $P<0·0005$), but it should be noted that the SPF was usually larger than the BLI, often by a factor of two or three.

Relationship between labelling indices from flow cytometry and immunohistochemistry

The pairs of results obtained by the two methods in each of the 50 patients studied immunohistochemically are shown in *Fig. 3* ($r_S=0·76$, $P<0·0005$). In each case, the difference (flow cytometric labelling index − immunohistochemical labelling index (ILI)) was calculated for analysis by the method of Bland and Altman[18]. The mean(s.d.) difference was $-0·325(2·30)$ per cent. The ILI for a tumour was marginally higher than the labelling index determined by flow cytometry but the difference was not significant ($t=1·20$, $P=0·24$, one-parameter t test). However, the relatively large standard deviation indicates that in individual tumours large variations in the labelling index as assessed by the two methods exist.

Relationship between kinetic parameters and clinicopathological data

The relationships between the derived kinetic parameters, tumour stage and oestrogen receptor expression are summarized in *Table 2*. Pathological staging information was available for 76 patients (90 per cent) in respect of

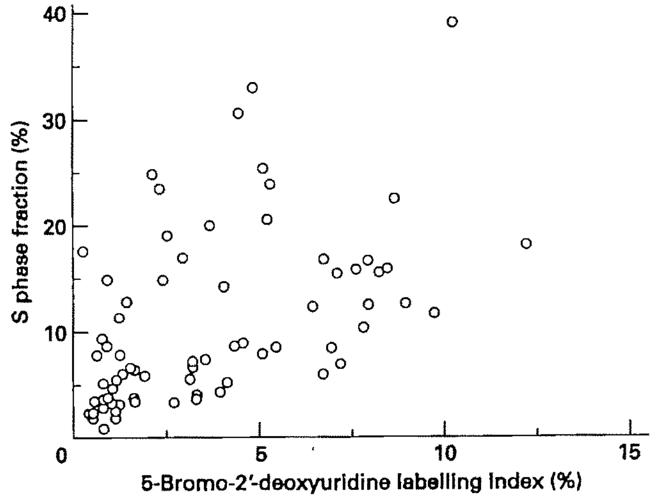

Fig. 2 5-Bromo-2'-deoxyuridine labelling index (BLI) *versus* S phase fraction (SPF) for each tumour in which both could be measured. Note different scales on x and y axes; SPF was usually substantially higher than BLI in the same tumour. ($r_S=0·69$, $P<0·0005$)

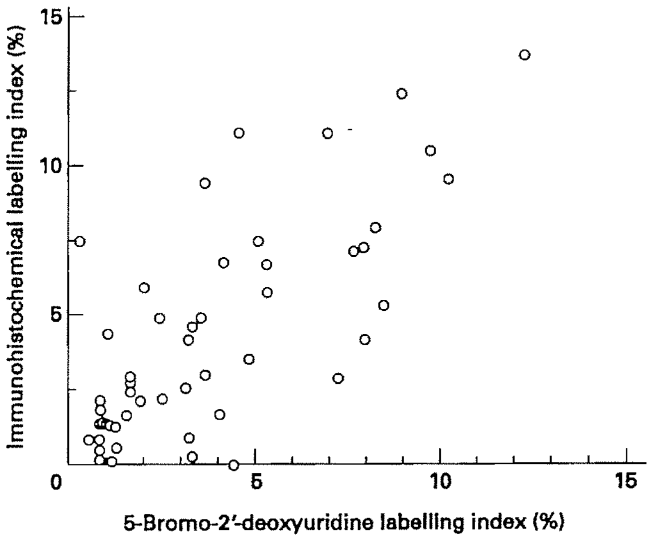

Fig. 3 5-Bromo-2'-deoxyuridine labelling index *versus* immunohistochemical labelling index for each of the tumours in which both could be measured. ($r_S=0·76$, $P<0·0005$)

Table 2 Relationship between kinetic parameters and clinicopathological variables

Parameter	n	BLI (%)	T_S (h)	T_{pot} (days)
Tumour size				
T_1	31	2·9	13·7	18·5
T_2	38	3·3	13·1	13·5
T_3	7	3·6	11·2	14·0
Nodal status				
N_0	37	3·2	12·1	17·7
N_1	32	4·2	13·7	12·5
Oestrogen receptor status				
Positive	16	1·2	12·8	36·5
Negative	12	4·0	14·3	12·4

Values are median. BLI, 5-bromo-2'-deoxyuridine labelling index; T_S, length of S phase; T_{pot}, potential doubling time

Table 3 Comparison of kinetic parameters in c-*erbB2* positive and negative tumours

	n	c-*erbB2*-negative	c-*erbB2*-positive	P*
BLI (%)	74	2·8	4·0	0·28
TLI (%)	74	2·7	1·9	0·63
ILI (%)	48	2·9	4·9	0·19
T_S (h)	58	13·6	13·6	0·48
T_{pot} (days)	58	19·6	13·7	0·77

Values are median. BLI, 5-bromo-2'-deoxyuridine labelling index; TLI, total labelling index; ILI, immunohistochemical labelling index; T_S, length of S phase; T_{pot}, potential doubling time. *Mann–Whitney U test

Table 4 Comparison of ploidy in c-*erbB2*-positive and negative tumours

	c-*erbB2*-negative	c-*erbB2*-positive
Diploid ($n=32$)	24 (75)	8 (25)
Aneuploid ($n=42$)	21 (50)	21 (50)

Values in parentheses are percentages. ($\chi^2=4·76$, 1 d.f., $P=0·03$)

tumour size, and in 69 patients (82 per cent) in respect of node involvement. No significant differences in labelling index, length of S phase or T_{pot} were observed between groups defined by nodal stage or tumour size, but in the 28 patients for whom oestrogen receptor status was known, oestrogen receptor-positive tumours were demonstrated to have lower labelling indices ($W = 222$, $P = 0{\cdot}03$, 95 per cent c.i. for difference in medians 0·3–4·0 per cent). The corresponding difference in doubling times in oestrogen receptor-positive tumours was not statistically significant ($W = 138$, $P = 0{\cdot}10$, 95 per cent c.i. for difference in medians −38–1·0 days).

Relationship between kinetic parameters and expression of c-erbB2

Some 74 of the tumours for which kinetic data were available (88 per cent) were assessed for c-*erbB2*; 29 of these (39 per cent) were found to be positive. *Table 3* gives the results of comparison of the cell kinetics of c-*erbB2*-positive and negative tumours. There was no significant difference between the cell kinetics of tumours that did or did not express c-*erbB2*. It has been noted previously that expression of c-*erbB2* is more common in aneuploid tumours, and a ploidy imbalance between any two groups of interest will bias their comparison because of the difference in the method of calculating labelling index in aneuploid and diploid tumours. In *Table 4* tumour ploidy and staining for c-*erbB2* are cross-tabulated. χ^2 analysis using these data showed that, in keeping with previous reports, aneuploid tumours are more likely to express c-*erbB2*. It is therefore important to look at the relationship between the ploidy-independent labelling indices TLI and ILI in the two c-*erbB2* groups (*Table 3*), but this did not increase the statistical significance of the relationship with labelling indices.

Discussion

Use of *in vivo* labelling with BrdU offers potential advantages over existing methods for estimating tumour cell kinetic parameters. Compared with the thymidine labelling index, it takes place *in vivo*, does not require several weeks for development of autoradiograms, and can be rapidly counted by flow cytometry. Unlike SPF, it relies on a functional measure of cell cycle activity. If these advantages are to be realized, kinetic measurements must be reproducible by this method. Within the present group of patients, a labelling index could be estimated in all but one, and this was achieved with a single 50-μm section in 85 per cent of tumours. This is one of the advantages of using embedded tumour as tumours are readily disaggregated. This modification of the original technique uses a minimum of tumour and provides parallel sections for histological or other studies. The results obtained are the same as those using disaggregated unembedded tumour[19]. The agreement between labelling indices calculated from flow cytometric analysis and those achieved by counting immunohistochemically stained specimens of the same tumours validates the method.

The reproducibility of the method can be tested by analysing consecutive sections. The coefficient of variation between sections was 12 per cent for BLI, and 13 per cent for T_S[19], which is small in relation to the intertumour variation. There was no significant difference in the value of BLI or T_S when a nuclear sample obtained by disaggregation of a tissue section was compared with one obtained by disaggregation of an unembedded segment of tumour as originally described by Dolbeare *et al.*[15]. The coefficient of variation for this comparison was 47 per cent for BLI, and 31 per cent for T_S. Since these represent spatially separate tumour samples the increase in coefficient of variation is presumably a result of intratumour heterogeneity. Interassay variation is small compared with both intratumour and intertumour variability. The presence of significant intratumour heterogeneity raises questions about the interpretation of measurements based on a single sample.

One study[14] used *in vivo* BrdU labelling to investigate the cell kinetics of human breast cancers in numbers comparable to those of the present series. Rew *et al.* studied 75 tumours. The range of values observed was similar to those seen in the present series, with a median value for BLI of 4·2 per cent (3·2 per cent in this series), and 8·7 h for T_S (12·0 h). The median value of T_{pot} reported (8·2 days) was shorter than that seen in this study (12·5 days) because of the higher labelling indices and shorter T_S. In accord with the present study there was no relationship between tumour size and labelling index, and tumour grade was unrelated to kinetic parameters.

Expression of the growth factor receptor oncoprotein c-*erbB2* is associated with a poor prognosis in breast cancer[20–22]. This might be because overexpression of such molecules confers a growth advantage on malignant cells. Rates of cell growth might be more rapid in tumours exhibiting overexpression; this has been the finding of some groups using SPF or TLI as measures of cellular proliferation[23–26]. In the present study, although there was a trend for all labelling indices to be higher in the c-*erbB2*-positive tumours, this was not statistically significant.

An advantage of the BrdU method is that it provides dynamic information about cell cycle transit rates. It is interesting that this parameter was not correlated with labelling index, as it was possible that tumours with a high labelling index would be those which demonstrated rapid cell cycle transit, in which case the dynamic information would be of no additional benefit. In a series of 56 gastric cancers, Ohyama *et al.*[27] found the converse, that T_S tended to lengthen as labelling index increased. This would result in a reduction of the overall kinetic effect of variation in labelling index, but the association in their data was weak, with T_S increasing by only about 2 h for every 10 per cent increase in labelling index. A stronger correlation was obtained by Wilson[28] for cancers of the head and neck, but no regression equation was given for these data. Within the present series, no differences were found in T_S between subgroups, however defined, which suggests that it may not be a biologically important variable.

The prognostic information to be gained from dynamic cell kinetics can only be assessed with lengthy follow-up, and with the number of tumours labelled here it is unlikely that significance will be achieved. The ability of any measure of cell proliferation to predict outcome in breast cancer is limited by at least two major factors. First, the process of tumour growth is a balance between cell growth and cell loss. BrdU labelling tells nothing of the latter, which may be much more potent in determining overall growth. Second, outcome is determined by the metastatic phenotype of the tumour, rather than its proliferative phenotype. Although prognosis is a common endpoint for the study of tumour cell kinetics, it seems unlikely that this will ever be clinically useful. The value of measuring cell proliferation derives from the potential to use these data to determine the likely sensitivity of the tumour to therapy, and as a tool for exploring tumour growth biology. The ability of cell kinetics to guide therapy is being addressed in the CHART (continuous, hyperfractionated, accelerated radiotherapy) trial of accelerated radiotherapy in head and neck tumours. The hypothesis is that tumours with a more rapid doubling time will benefit more from hyperfractionated radiotherapy, although the preliminary results of the trial[29] do not support this. The use of kinetic data to address the question of whether c-*erbB2* may be acting as a mitogen for breast cancers, giving them a growth advantage, is an example of the way in which improved methods for the study of cell kinetics may be able to help the understanding of what makes tumours grow abnormally.

Acknowledgements

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Short note

Ultrasonographically guided excisional biopsy of non-palpable breast lesions

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Excision of small non-palpable breast lesions can be difficult and may result in the unnecessary removal of excessive surrounding breast tissue[1]. With this in mind a simple excisional biopsy technique for such lesions has been developed which employs intraoperative ultrasonography to guide the extent of excision.

Patients and methods

Under local anaesthesia a periareolar incision of approximately 30 mm was made in the appropriate breast quadrant (alternative incisions may be employed to achieve the same end). The subcutaneous connective tissue was dissected from the parenchyma by blunt dissection to create a pocket into which a sterilizable high-resolution ultrasound transducer was inserted. The ultrasound probe was used to determine the depth of the lesion and to guide the surgeon towards the target zone. To facilitate imaging the cavity was filled with a sterile solution.

Once the site of the lesion in the parenchyma had been localized, it was exposed with the help of Kocher's forceps and small retractors. This helped to delineate the zone of incision and to determine the depth of the lesion. It also assisted the surgeon when deciding which type of excision should be performed: enucleation of the lesion (in the case of fibroadenoma) or excision of surrounding parenchyma (in the case of lesion with poorly defined borders, such as neoplasm or fibrocystic mastopathy).

Before being sent to pathologist, the specimen was scanned again to ensure complete removal by comparing the postoperative images with ultrasonographic scans obtained before and during operation. (To facilitate this, the specimen may be placed in the finger of a surgical glove filled with physiological solution.)

Results

Using this technique 27 patients underwent excisional biopsy for non-palpable breast lesions. Twenty-nine lesions were biopsied. The mean diameter of lesions as assessed by preoperative ultrasonography was 10·9 mm; that of subsequent biopsy was 17·2 mm and of histologically evaluated lesions 8·9 mm.

Histological examination revealed fibrocystic mastopathy with apocrine metaplasia in 18 cases, fibroadenoma in eight, invasive ductal carcinoma in two and atypical ductal hyperplasia in one.

Discussion

This technique is similar but not identical to that described by Schwartz *et al.*[2,3]. The method has the following advantages: (1) it allows greater precision in removing the mass as the surgeon is constantly guided by the scanner; (2) the accuracy of the biopsy may be checked immediately by examining the removed specimen with the ultrasound probe; (3) it avoids the needless sacrifice of healthy breast tissue; and (4) it permits examination of the breast immediately after biopsy.

The use of very small and more manageable transducers with higher resolution may be of value. However, the results from this preliminary series suggest that this technique is worthy of further study and comparison with other diagnostic procedures.

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Short note

'Soup ladle' autotransfusion

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Autotransfusion is the collection and reinfusion of the patient's own blood. This technique can help in response to the increasing demand for blood and the heightening awareness of transfusion morbidity[1]. A simple, low cost, perioperative autotransfusion technique that can be easily practised by all surgeons is described.

Patients and methods

In the presence of haemoperitoneum, autotransfusion is performed using the following equipment: one sterile small soup ladle or gallipot; one sterile kitchen funnel; a 250- or 500-ml glass bottle (with rubber top) containing 60 or 120 ml acid–citrate–dextrose anticoagulant solution respectively; a filter made from two or three thicknesses of sterile gauze; and an in-line micropore filter (to lower the risk of contamination and sepsis) and intravenous tubing for transfusion. The sterile bottle with anticoagulant solution is opened and the funnel with the gauze filter is placed in the mouth of the bottle. With the patient in the Trendelenburg position, a peritoneal opening is made which is large enough to collect the blood with the ladle. This blood is poured through the filter and the funnel into the bottle. The assistant raises the peritoneum to avoid blood spillage from the peritoneal cavity. When the bleeding is controlled, residual haemoperitoneum is removed from the abdominal cavity. The final collection of blood is facilitated by changing the patient to the reverse Trendelenburg position. A sample of blood is evaluated for haemolysis. If the blood is not haemolysed, the blood bottles are stoppered and the anticoagulated blood is transfused with a normal giving set.

Results

From January 1992 to December 1993, a total of 27 patients with haemoperitoneum were admitted. In five patients the haemoperitoneum was because of traumatic splenic rupture and in the remaining 22 to ruptured ectopic tubal pregnancy. Autotransfusion was possible in 18 patients. In eight of the nine in whom autotransfusion was not possible, haemolysis was present; in the remaining patient there was only minimal haemoperitoneum. A significant difference in duration of symptoms was noted between patients with haemolysis (mean(s.d.) 7·37(6·46) days) and those without haemolysis (mean(s.d.) 3·11(2·27) days) ($t = 2{\cdot}52$, 24 d.f., $P < 0{\cdot}05$). Of the 18 patients in whom autotransfusion was possible, there were two men and 16 women; the mean(s.d.) age was 31·72(10·49) years. Splenectomy was performed in four patients, monolateral salpingectomy in 13, and bilateral salpingectomy in one. Patients received a mean(s.d.) 1014(348) ml of blood. Mean(s.d.) haemoglobin level of autotransfused blood was 7·7(2·7) g/dl. Mean(s.d.) venous preoperative haemoglobin content was 7·5(3·3) g/dl; all patients received only autologous blood. There was neither complication nor adverse reaction related to autotransfusion. Of the 18 patients given autotransfused blood, one died 4 days after surgery; this was a 10-year-old boy who had undergone splenectomy and was in coma because of injury to the head. Mean(s.d.) postoperative haemoglobin level, checked 3 days after surgery, was 8·6(2·8) g/dl.

Discussion

If a patient is haemodynamically stable with no significant anaemia and the volume of haemoperitoneum is less than 500 ml, crystalloid resuscitation is sufficient. However, if transfusion is indicated, autotransfusion is the safest method of blood replacement. Advantages include blood availability and compatibility, absence of risk of transmissible diseases, and improved acceptance by patients, especially those whose religion or culture prohibit donor transfusion. Complications of autotransfusion include haematological changes, alteration in coagulation and sepsis. To reduce the risk of haemolysis, which increases with the duration of symptoms, laboratory examination for the presence of free haemoglobin should always be performed. Autotransfusion should not exceed 3000–4000 ml to avoid coagulopathy and it should be accomplished within 4 h of collection. It should never be used if contamination is suspected[2,3] or in patients with coagulopathy. In the past 70 years different devices for autotransfusion have been developed, but all are costly and difficult to manage[4,5]. 'Soup ladle' autotransfusion, however, is simple, cheap, and can be used in small hospitals, such as those in rural areas in developing countries.

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Short note

Midgut volvulus in children

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Midgut volvulus secondary to intestinal malrotation usually presents within the first month of life, typically with persistent bilious vomiting[1]. Diagnostic delay may result in midgut infarction and death. Malrotation may, however, remain quiescent during early childhood and present later in life. Over a 15-year interval, seven patients presented with midgut volvulus well beyond infancy. These cases illustrate important features in presentation which may not be familiar to general surgeons in district general hospitals who may have to deal with this problem.

Case reports

A summary of the presentation, investigation, and treatment of these patients is given in *Table 1*. One child presented with haemodynamic collapse secondary to complete midgut infarction. The remaining six all presented with recurrent abdominal pain and vomiting, bile-stained in five cases. Four patients had clinical evidence of malnutrition and poor weight gain and diagnosis was delayed in five because of a low index of suspicion. The majority of patients had few abdominal signs on initial presentation.

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Discussion

Midgut volvulus secondary to intestinal malrotation is a well recognized paediatric surgical emergency, typically presenting with bile-stained vomiting in the neonatal period. Fifty per cent present within the first week of life and an additional 30 per cent within the first month[1]. Although the risk of volvulus secondary to intestinal malrotation diminishes in patients older than 1 month it has been documented during childhood, adolescence and adulthood[1–4].

During foetal development, the midgut, supplied by the superior mesenteric artery, rotates 270° anticlockwise as it returns from the extraembryonic coelom such that the caecum comes to lie in the right iliac fossa[5]. In the commonest variant of malrotation, the duodenojejunal junction lies at, or to the right of the midline and the caecum is placed in the right upper quadrant of the abdomen. As a result the small bowel is suspended from a narrow based mesentery extending from the duodenojejunal flexure to the terminal ileum with a subsequent potential for small bowel volvulus[6].

Surgical intervention in the form of Ladd's procedure involves a laparotomy via a supraumbilical incision. The volved segment is rotated anticlockwise and any obstructing folds of peritoneum (Ladd's bands[7]) are divided. The duodenojejunal junction is placed in the right gutter of the abdomen with the caecum being placed in the left upper quadrant, thus creating a longer mesentery for the midgut and removing the potential for further volvulus.

Presentation in older children differs from that in neonates. Vomiting is typically bilious and is frequently accompanied by generalized abdominal pain[8,9]. These symptoms may be chronic and intermittent, frequently leading to multiple admissions, due to partial twisting of the midgut segment. The latter may result in mesenteric venous engorgement, mesenteric lymphadenopathy and intestinal oedema, all common findings at laparotomy[10,11]. It has been suggested that these factors contribute to the malnourished state commonly found in these children.

Table 1 Summary of cases

Patient no.	Age (years)	Sex	Previous admissions	Symptoms	Signs	Investigations	Treatment	Outcome
1	11	M	0	Bilious vomiting Abdominal pain	Abdominal tenderness	Upper GI contrast study	Ladd's procedure	Uneventful
2	3	F	0	Vomiting Abdominal pain Fresh melaena	Hypotension Tachycardia Tenderness	Abdominal radiograph	Emergency laparotomy and Ladd's procedure	Uneventful
3	6	M	1	Bilious vomiting Abdominal pain	Dehydration Malnourishment	Upper GI contrast study	Ladd's procedure	Uneventful
4	5	F	1	Bilious vomiting Abdominal pain	Malnourishment	Upper GI contrast study	Ladd's procedure	Uneventful
5	11	M	5	Bilious vomiting Abdominal pain	Dehydration Malnourishment	Upper GI contrast study	Ladd's procedure	Uneventful
6	7	M	4	Bilious vomiting Abdominal pain	Dehydration Malnourishment	Upper GI contrast study	Ladd's procedure	Uneventful
7	8	M	3	Haemodynamic collapse	Rigid abdomen	Abdominal radiograph	Emergency laparotomy for complete midgut infarction	Died

GI, gastrointestinal

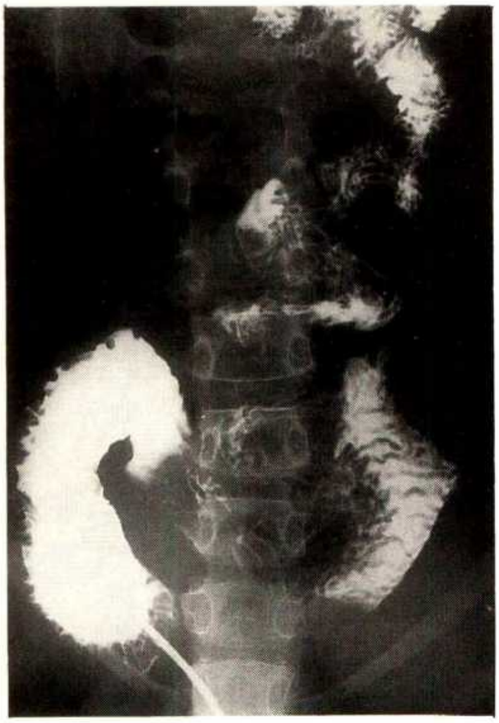

Fig. 1 Barium follow through showing midgut volvulus

Abdominal radiography can be useful. A relatively gasless abdomen is an indication that volvulus may have occurred. However, by contrast, a caecal gas shadow in the right iliac fossa makes the diagnosis of malrotation unlikely[12,13]. Rarely, however, the caecum may be excessively mobile and, despite malrotation and volvulus, may still be placed in the right iliac fossa, as in one of the present cases.

Contrast enemas have been used to establish the diagnosis but excessive mobility of the caecum may lead to diagnostic confusion. The investigation of choice is an upper gastrointestinal contrast study which will confirm the diagnosis[14] (*Fig. 1*).

Midgut volvulus is rare but potentially life threatening. Children who present with bile-stained vomiting in association with abdominal pain, particularly if intermittent, should have this diagnosis excluded.

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Pattern of recurrence after oesophageal resection for cancer: clinical implications

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Patterns of disease recurrence were reviewed in 108 patients who had curative resection for squamous cell cancer of the thoracic oesophagus. At a median follow-up of 20 months, 56 patients (52 per cent) had recurrence. Most presented within 2 years. Extrathoracic recurrence was found in 41 per cent of patients and intrathoracic recurrence in 25 per cent. Systemic organ metastases (26 per cent) were as frequent as intrathoracic recurrences. Twelve patients (11 per cent) developed cervical lymph node (CLN) recurrence; their mean time to recurrence was 12·6 months, compared with 13·1 months for recurrence at locations other than the neck ($P = 0{\cdot}8$). Median survival was 23 and 13 months respectively ($P = 0{\cdot}27$). Preoperative chemotherapy lowered the recurrence rate from 60 per cent to 30 per cent, ($P = 0{\cdot}01$) but did not affect survival. The addition of cervical lymphadenectomy would benefit few patients and must be counterbalanced with increased morbidity and cost. The frequency of systemic organ metastases calls for further investigation of the possible benefits of chemotherapy.

Surgery is still the main treatment for oesophageal cancer because it provides better palliation and a chance of cure. Advances in surgical technique and perioperative management have made oesophageal resection an operation of acceptable risk[1,2]. Long-term survival has remained poor. Even after apparently curative surgery, a large number of patients will experience disease recurrence. Attempts have been made to improve outcome by combining different treatment modalities and by more aggressive resection with extended lymphadenectomy. Studies on the time and location of recurrent disease have not been adequately documented. The authors have reviewed their experience of curative resection for squamous cell carcinoma of the thoracic oesophagus with the aim of determining the pattern and time of recurrence, factors which may affect the incidence of recurrent disease, treatment options, and implications for future management strategies, with special regard to cervical lymphadenectomy and adjuvant treatments.

Patients and methods

Between June 1987 and December 1993, 594 unselected patients with carcinoma of the oesophagus or gastric cardia were managed in this department. Squamous cell carcinomas were found in 435 patients (73 per cent) and 96 patients (16 per cent) had adenocarcinomas. Other less common tumours were identified in 63 patients (11 per cent). Of the 435 patients who had squamous cell cancers, 30 had either double tumours, other synchronous or metachronous cancers and were excluded from this study. In the remaining 405 patients, the cervical oesophagus was involved in 18, the upper third of the thoracic oesophagus in 32, the middle third in 268, and the lower third in 87.

The main treatments given to the 387 patients with intrathoracic squamous cell carcinoma are listed in *Table 1*. Resection was performed in 284 patients (73 per cent). Both the tumour and the adjacent lymph nodes were removed completely. Resection was considered curative when the tumour was confined to the oesophagus, and the adjacent lymph nodes were either uninvolved or were less than 2 cm in diameter, discrete, and within the vicinity of the primary tumour. Resection was palliative when there was tumour infiltration beyond the oesophagus into mediastinal organs, when there were gross lymph node metastases, or when residual tumour was confirmed or likely after resection.

The resection techniques have been described elsewhere[3,4] In the abdomen, enlarged lymph nodes were resected within an anatomical area bounded by the superior border of the pancreas, splenic hilus, diaphragmatic hiatus and the hepatoduodenal ligament. The lesser omentum was removed and the left gastric artery nodes resected to the origin of the artery. In the thorax, the oesophagus was removed in continuity with paraoesophageal, subcarinal, parabronchial, paratracheal lymph nodes and the thoracic duct. The left recurrent laryngeal nerve nodes were not routinely removed. The thoracic aorta, pericardium and pulmonary veins were also bared of connective tissue. In resections without a thoracotomy, only paraoesophageal nodes that could be resected under vision were removed. Cervical lymphadenectomy was not practised

Preoperative chemotherapy was given to 30 patients as part of an ongoing prospective randomized study It comprised two courses of cisplatin (100 mg/m^2 on day 1) and 5-fluorouracil (5-FU) (500 mg/m^2 on day 1 to day 5) given at 3-week intervals followed by resection 2 weeks later. Postoperative radiotherapy was given to patients as part of a prospective randomized trial in

Table 1 Main treatment of 387 patients with squamous cell carcinoma of the intrathoracic oesophagus

Treatment	No. of patients
Resection	284 (73)
Split sternum oesophagectomy	9
Transhiatal oesophagectomy	47
Three-phase oesophagectomy	40
Lewis–Tanner oesophagectomy	169
Oesophagogastrectomy	17
Staged resection	2
Bypass	60 (16)
Exploration	6 (2)
Radiotherapy	5
Chemotherapy	2
Laser treatment	4
Intubation	17
No intervention	9

Values in parentheses are percentages

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the earlier part of this series that was completed in December 1989[5]. After this study, radiotherapy was given only to patients with histological evidence of tumour at the resection margin. A total of 34 patients received postoperative radiotherapy.

Resection was curative in 128 patients (45 per cent). The 30-day mortality rate was 3·9 per cent (five patients), and hospital mortality rate was 8·6 per cent (11 patients). Of the survivors, nine patients were lost to follow-up. The remaining 108 patients were seen every second week for 2 months and monthly thereafter for 1 year, then at 3-month intervals. At each follow-up, a complete physical examination was performed, together with appropriate investigations as indicated when recurrence was suspected.

Extrathoracic recurrence included cervical and abdominal lymph node metastases, peritoneal or systemic (liver, lung, bone, skin, other sites) metastases. Intrathoracic recurrence included tumour in the trachea or bronchi, in the oesophageal substitute or mediastinum. Anastomotic recurrences refer to the area between the proximal oesophagus and the oesophageal substitute, and were diagnosed by endoscopic biopsy.

When recurrence was evident in two anatomical locations, both were considered to have developed synchronously if detected within 30 days of each other.

All data were entered prospectively into a computer. Statistical analyses included the Student's t test, χ^2 test with Yates' correction or Fisher's exact test when appropriate. Patient survival was calculated by the Kaplan–Meier method, and the difference between groups was tested non-parametrically by the generalized Wilcoxon method. Statistical significance was taken at $P<0.05$. The programme used was the Statistical Package for the Social Sciences (SPSS-X version 3.1; SPSS, Chicago, Illinois, USA).

Results

The mean age of the 108 patients was 64 (range 47–79) years, with a male to female ratio of 3·7:1. The upper, middle and lower thirds of the oesophagus were involved in 3, 76 and 29 patients respectively. Operative staging showed that seven patients had stage I, 33 stage IIa, 14 stage IIb and 54 stage III disease[6]. The median follow-up period was 20 (range 3–81) months.

Of the 108 patients, 52 (48 per cent) had no recurrent disease (three died from unrelated causes); 56 patients (52 per cent) had tumour recurrence and all except one died. Cachexia related to cancer was the primary cause of death in 45 patients. Six patients died from tracheobronchial obstruction due to tumour; three of these had evidence of other mediastinal disease – one had pulmonary metastases and two had cervical lymph node metastases. Three patients died from bronchopneumonia and one patient had spinal metastases and developed tetraplegia before death.

The median survival of patients who had a curative resection was 23 months. The 1-, 2-, 3-, 4-, 5-year survival rates were 65, 48, 36, 34 and 32 per cent respectively.

The pattern of tumour recurrence in the 56 patients is shown in *Tables 2* and *3*. Extrathoracic disease was more common than intrathoracic recurrence. Systemic organ metastases were as frequent as intrathoracic recurrences. The level of the primary tumour had no relationship to the distribution of recurrences at different locations.

The timing of recurrence for the 56 patients is shown in *Fig. 1*. The median delay before recurrence was 10 months and most recurred within 2 years (88 per cent). There was no difference in survival time between patients with intrathoracic disease alone, extrathoracic disease alone or both.

Twelve patients (11 per cent) developed recurrence in the cervical lymph nodes (CLNs) (*Tables 3* and *4*), after a mean of 12·6 months, not significantly different from patients with recurrence at other locations and no neck disease (13·1 months) ($P=0.8$). In three patients with metachronous tumour with CLN recurrence, the

Table 2 Pattern of recurrence in 56 patients after 'curative' resection

Site of recurrence	Upper ($n=1$)	Middle ($n=39$)	Lower ($n=16$)	Total ($n=56$)
	No. of patients with recurrence			
Extrathoracic alone	0 (0)	20 (51)	9 (56)	29 (52)
Intrathoracic alone	0 (0)	8 (21)	4 (25)	12 (21)
Extrathoracic and intrathoracic	1 (100)	11 (28)	3 (19)	15 (27)

Values in parentheses are percentages. Patients are grouped according to level of primary tumour (upper, middle or lower third of oesophagus)

Table 3 Sites of recurrence in 56 patients after 'curative' resection

Site of recurrence	Upper ($n=1$)	Middle ($n=39$)	Lower ($n=16$)	Total ($n=56$)
	No. of patients with recurrence			
Extrathoracic	1 (33)	31 (41)	12 (41)	44 (41)
Cervical lymph node	1 (33)	7 (9)	4 (14)	12 (11)
Abdominal lymph node	0 (0)	4 (5)	1 (4)	5 (5)
Systemic organs	0 (0)	20 (26)	8 (28)	28 (26)
Lung	0	11	2	13
Liver	0	8	3	11
Bone	0	5	2	7
Soft tissue and skin	0	3	2	5
Other locations*	0	2	1	3
Intrathoracic	1 (33)	19 (25)	7 (24)	27 (25)
Tracheobronchial tree	1	8	2	11
Intrathoracic oesophageal substitute	0	4	5	9
Mediastinal recurrence†	0	11	2	13
Upper anastomosis	0	5 (7)	1 (3)	6 (6)

Values in parentheses are percentage with recurrence of total number of patients who underwent 'curative' resection of tumour in the upper ($n=3$), middle ($n=76$) and lower ($n=29$) third of the oesophagus (total 108). *Including kidney, adrenal gland. †Manifested as mediastinal lymph node or mass on computed tomography

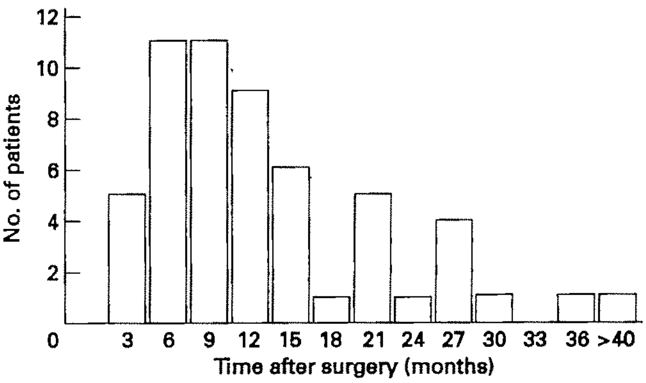

Fig. 1 Time to detection of disease recurrence after 'curative' resection in 56 patients. Median time was 10·3 months

appearance of CLN recurrence preceded recurrence at other sites by 5, 14 and 16 months. The median survival time in patients who had CLN recurrence was 23 months compared with 13 months in patients with no CLN recurrence but with recurrence at other locations ($P = 0{\cdot}27$).

Patterns of intrathoracic recurrence are shown in *Tables 3* and *5*. Twenty-seven patients developed such recurrences, of whom 13 had no extrathoracic disease.

The relation between anastomotic recurrence and proximal resection margin measured at operation is shown in *Table 6*.

Factors that may affect the incidence of recurrence were studied (*Table 7*). Only preoperative chemotherapy had a beneficial effect. The recurrence rate was reduced from 60 to 30 per cent in those who received chemotherapy ($P = 0{\cdot}01$). Survival, however, was not significantly affected by chemotherapy. The three patterns of recurrence, i.e. extrathoracic alone, intrathoracic alone and both, were not influenced by the factors studied.

Response of recurrent disease to treatment was assessed by individual sites. Radiotherapy and chemotherapy were used alone, or in combination, in the treatment of eight of the 12 patients with CLN metastases. Only one had a good response with combined therapy and is still alive 4·5 years later. A partial response, with reduction in node size, was noted in two other patients.

Of the 11 patients with tracheobronchial recurrence, one had tumour regression with radiotherapy but a fistula developed between the trachea and the intrathoracic stomach. Laser was employed in five patients to achieve airway patency. Chemotherapy was used in two patients with no response.

Anastomotic recurrences producing significant dysphagia were treated with simple dilatation in two patients, and radiotherapy in one. The response was poor although food passage was easily maintained by dilatation until death from metastases.

Table 4 Cervical lymph node recurrence

	Location	Patients ($n = 12$)
Cervical lymph nodes alone	Neck	4
Cervical lymph nodes and other sites (synchronous)	Intrathoracic oesophageal substitute	1
	Upper anastomosis	1
	Skin	2
	Tracheobronchial tree	1
Cervical lymph nodes and other sites (metachronous)*	Tracheobronchial tree	2
	Intrathoracic oesophageal substitute, mediastinal lymph node and lung	1

*In all three patients cervical lymph node recurrence preceded recurrence at other sites

Table 5 Patients with intrathoracic recurrence

	Location	Patients ($n = 27$)
Intrathoracic alone	Tracheobronchial tree, intrathoracic oesophageal substitute, mediastinal lymph nodes	13
Intrathoracic and other sites (synchronous)	Cervical lymph nodes	2
	Skin	1
	Lung	2
	Lung, liver, abdominal lymph node and bone	1
	Upper anastomosis	3
Intrathoracic and other sites (metachronous)*	Liver	1
	Lung	1
	Cervical lymph nodes	2
	Cervical lymph nodes and lung	1

*Intrathoracic recurrences preceded the appearance of liver or lung metastases in two patients and appeared after other sites of recurrence in the other three patients with cervical lymph node recurrences

Table 6 Relation between anastomotic recurrence and proximal resection margin measured at operation

Proximal resection margin *in vivo* (cm)	No.	Anastomotic recurrence
2–4	2	1 (50)
4–6	16	3 (19)
6–8	24	1 (4)
8–10	17	0 (0)
>10	30	1 (3)*
Margin not measured	19	0 (0)
Total	108	6 (6)

Values in parentheses are percentages *This patient's resection margin was 19 cm. Histological examination revealed metastatic tumour in the muscle wall at the margin. The patient declined postoperative radiotherapy

Table 7 Factors which may affect the incidence of recurrence

	No recurrence ($n = 52$)	Recurrence ($n = 56$)	P
Mean(s.d.) age (years)	65(8)	63(8)	0·20†
Sex ratio (M:F)	40:12	44:12	0·70‡
Level of tumour			
Upper third	2	1	0·32‡
Middle third	37	39	
Lower third	13	16	
Resection via thoracotomy			
Thoracotomy	41	43	0·8‡
No thoracotomy	11	13	
Differentiation of tumour*			
Well	14	19	0·91‡
Moderate	16	18	
Poor	9	10	
Depth of invasion*			
Short of adventitia	8	13	0·64‡
Adventitia involvement	19	24	
Lymph node status			
Positive	13	20	0·23‡
Negative	39	36	
Postoperative radiotherapy			
Radiotherapy	14	20	0·33‡
No radiotherapy	38	36	
Preoperative chemotherapy			
Chemotherapy	21	9	0·01‡
No chemotherapy	31	47	

*Only patients who had complete data on differentiation and depth of invasion of tumour were included in the analysis. †Student's t test; ‡χ^2 test

Radiotherapy produced pain relief in two patients with bone metastases. Laminectomy resulted in temporary neurological improvement in one patient with spinal cord compression.

Most patients with recurrence in systemic organs received no definitive treatment and were managed symptomatically.

The mean time from detection of recurrence to death was 4 months.

Discussion

Recurrence developed early even after apparently curative resection for oesophageal cancer. The 5-year survival rate was only 32 per cent. Two-thirds of patients with recurrence presented within 1 year and nearly all within 2. Efforts to improve outcome have been attempted using adjuvant therapy and more extensive surgery, including three-field (bilateral cervical, mediastinal and abdominal) dissection, popularized in Japan[7].

The addition of cervical lymphadenectomy to conventional thoracoabdominal lymph node dissection remains controversial[8]. The overall rate of CLN involvement has been documented by three-field dissection and is approximately 30 per cent[9,10]. In relation to the level of primary tumour, CLNs were involved in 60, 20 and 12·5 per cent of upper, middle and lower third tumours respectively[9–11]. However, the incidence of lymph node involvement at the time of resection may not correspond to subsequent clinically significant recurrence. It has been documented that CLN metastases were found in 14·3 per cent of patients undergoing three-field dissection but recurrence was detected later in only 8·6 per cent. In the cervicothoracic nodes (which transgressed both the cervical region and the upper mediastinum), the respective figures were 37·1 and 10 per cent[12]. Without cervical lymphadenectomy, a similar proportion of patients developed CLN recurrence (11 per cent) in the present series. If cervical dissection had been performed, this recurrence rate might have been lower. Even so, only 11 per cent of patients could have profited. Moreover, of the 12 patients who had CLN recurrence, five had synchronous recurrence at other sites. The higher frequency of systemic organ metastases further limits the role of additional neck dissection. By comparison, a more substantial number of patients developed intrathoracic recurrence despite mediastinal lymphadenectomy, 48 per cent of whom did not have disease elsewhere. Tumour invasion into the tracheobronchial tree or the oesophageal substitute is usually symptomatic and difficult to manage compared with CLN recurrence.

If CLN recurrence could be the source of tumour cells for distant metastasis, then lymphadenectomy may be of use[13]. This mechanism of tumour spread is considered exceptional[14,15]. In the present series, CLN recurrence preceded mediastinal or distant metastasis in only three patients. Few patients would benefit even if the hypothesis were true.

Any potential benefit of cervical lymphadenectomy must be weighed against the lengthened operating time and the associated morbidity, such as recurrent laryngeal nerve palsy[9,16,17]. Favourable outcome has been variably reported in patients with early or advanced disease and multi-institutional studies have been indecisive on the superiority of three-field dissection[7,18,19]. The lack of a well conducted, randomized trial is the unanimous criticism voiced against extended lymphadenectomy.

As regards pathological factors, blood vessel and lymphatic invasion documented on resected specimens has been linked to systemic organ recurrence and lymphatic recurrence respectively[20]. The number of positive nodes also influenced the recurrence rate and the disease-free survival[21]. In this study, pathological factors were not useful in predicting recurrence.

Disease recurrence may be altered by adjuvant treatment. Preoperative chemoradiation improved local control of mediastinal disease[22,23]. Overall survival, however, was no better because of the high rate of distant metastases. In this retrospective study, preoperative chemotherapy significantly reduced the recurrence rate. Neither the pattern of recurrence, nor survival was altered. However, preliminary data from a prospective randomized trial suggest a survival benefit for responders to chemotherapy, who tend to be those with early disease suitable for curative surgery[24].

The lack of benefit of postoperative radiotherapy in local control and survival in patients after curative resection shown in the authors' previous prospective, randomized trial was reaffirmed in this study. Local recurrence, especially in the tracheobronchial tree, was reduced only in patients who had palliative resection with residual tumour in the mediastinum after surgery[5].

Tracheobronchial recurrence leads to airway obstruction. Laser therapy provides good temporary symptomatic relief. Additional chemotherapy or radiotherapy may be offered to those whose condition is satisfactory[25].

The authors previously reported that anastomotic recurrence was a function of the length of resection margin obtained at resection[26,27]. The results of the present study consolidate the earlier findings. A resection margin of 10 cm or more should be aimed for.

The treatment of recurrent disease was disappointing. There is no evidence that currently available treatment can prolong survival. In a prospective follow-up of patients using routine computed tomography, Barbier and colleagues[28] showed that the symptom-free interval exceeded the tumour-free interval by 4 months. Earlier detection of asymptomatic recurrences apparently had no impact on outcome. Treatment of recurrence should aim at palliation and improving the quality of the remaining life.

To reduce recurrence and improve survival remains a challenge. While surgery carried out with low morbidity and mortality plays an essential part in the management of local disease, it seems that the frequency of metastatic disease calls for more effective chemotherapeutic agents for systemic treatment. The addition of cervical dissection would benefit only a very few patients and must be weighed against increased morbidity and cost.

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Short note

Randomized trial of fibrin tissue glue for low output enterocutaneous fistula

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The healing of enterocutaneous fistulas depends on the patient's nutritional status, the volume of discharge and the patency of the distal bowel. Sometimes, despite adequate nutrition and reducing discharge, the fistula is slow to heal completely[1].

Fibrin tissue glue is a biological product that can stimulate wound healing[2–4]. Its use to enhance the closure of low-output enterocutaneous fistula has seldom been described. This report compares outcome in six patients with low-output enterocutaneous fistula in whom fibrin glue was applied with that in seven similar patients treated conservatively.

Patients and methods

Thirteen patients with a variety of low-output enterocutaneous fistulas that had been present for 2–4 weeks were included in the study (*Table 1*). All had conservative treatment with total parenteral nutrition (TPN). In all cases, fistula discharge was less than 20 ml per day, no mucosal eversion was present on the abdominal wall and there was no evidence of intra-abdominal abscess. The patients were randomly divided into two groups. Six patients had fibrin tissue glue infused into the fistula tract (group 1) and the other seven acted as controls (group 2). The fibrin tissue glue was prepared using 1 unit cryoprecipitated plasma, 5 ml thrombin, 4 ml calcium chloride and 1 ml normal saline[5]. After informed consent, 15 ml glue was infused into the fistula tract of patients in group 1 and a compressive dressing was applied to the abdomen. The fibrin glue solidified immediately on infusion. If the discharge recurred, the glue was again infused after 3 days.

Fistula closure time was compared between the two groups. Statistical analysis was performed using Student's unpaired *t* test.

Table 1 Clinical details and time to healing in patients who had fibrin glue (group 1) for enterocutaneous fistula and in controls (group 2)

	Group 1 ($n=6$)	Group 2 ($n=7$)
Sex ratio (M:F)	3:3	4:3
Age (years)*	46(3)	42(5)
Diagnosis		
Postgastrectomy	1	2
Postenterorrhaphy	1	2
Non-healing jejunostomy	1	1
Colonic fistula	1	0
Post acute pancreatitis	2	2
Duration of fistula before the trial (days)*	18(2)	19(2)
Time for healing (days)*	2(0·4)	13(2)†

*Values are mean(s.e.m.). †$P < 0·01$ (Student's unpaired *t* test)

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Results

There were no adverse reactions to fibrin glue. All the fistulas in group 1 healed within 4 days. Two patients required a second infusion on the third day before complete closure, but all were discharged within 1 week. There were no recurrences after a minimum of 1 year of follow-up.

Patients in group 2 received TPN alone. Fistula healing took between 7 and 21 days, significantly longer than in group 1 ($P < 0·01$).

Discussion

The use of fibrin tissue glue for low-output enterocutaneous fistula in this study speeded healing and reduced hospital stay. It is not possible to use fibrin glue for high-output fistulas but, if the discharge decreases after conservative treatment, the glue might be beneficial to speed final healing. If the initial application of fibrin glue does not close the fistula, it can be used again. Optimal conditions for fistula healing include no distal obstruction, no intra-abdominal abscess and no mucosal eversion.

Fibrin tissue glue has been shown in this study to be safe and effective for patients with stable, low-output, enterocutaneous fistulas.

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Short note

Management of intestinal obstruction after gastrectomy for carcinoma

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Intestinal obstruction after operation for gastrointestinal cancer may be due to postoperative adhesions, a focal, potentially resectable, malignant deposit or diffuse carcinomatosis[1,2]. It is commonly assumed that the obstruction is due to advanced malignancy and that death is inevitable.

This study aimed to determine the benefits of further surgical treatment in terms of quality of life in patients who presented with intestinal obstruction following operation for primary gastric cancer.

Patients and methods

Between January 1980 and December 1993, 85 patients (6·7 per cent of all those undergoing operation for gastric cancer) with symptoms of partial or complete intestinal obstruction were admitted. Of these 85 patients, 50 underwent laparotomy because the obstruction did not resolve with conservative treatment. Of the remaining 35 patients, the obstruction resolved spontaneously in 18; laparotomy was not deemed appropriate in 17 because of uncontrolled ascites or cachexia. Patients with intestinal obstruction due to other cancers, those undergoing emergency surgery and those with obstruction noted within the first 2 months after operation were not included in the analysis.

Results

The cause of the intestinal obstruction was diffuse peritoneal metastasis in 28 patients (56 per cent), local recurrence in 12 (24 per cent) and benign adhesions in ten (20 per cent). There was no correlation between the clinicopathological appearance of the primary tumour and the cause of obstruction. Of 40 patients in whom obstruction was due to recurrence, palliative surgery was not possible in nine because of advanced abdominal metastatic disease. Twenty-four patients who underwent bypass surgery, colostomy, resection or catheter jejunostomy had symptomatic relief. Seventeen patients increased their oral food intake, and 17 were discharged from hospital, at least temporarily (*Table 1*). There were no complications in the ten patients operated on for obstruction due to benign adhesions.

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Discussion

Peritoneal metastases are the most common form of recurrence in patients who have undergone gastrectomy for cancer[3,4]. However, it should be noted that in the present series intestinal obstruction had a benign cause in 20 per cent of patients, although the preoperative diagnosis was quite difficult. The principal aim in the management of patients with terminal cancer is to relieve symptoms so that they may return home to their families for as long as possible. Even in patients with recurrent obstruction, surgical relief of the obstruction allowed the patients who would have died in hospital to return home and contributed in many to the improvement in quality of life. Accordingly it is suggested that active surgical intervention is recommended even for terminally ill patients when symptomatic relief cannot be obtained with conservative management.

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Table 1 Outcome after surgical treatment for malignant bowel obstruction

	Bypass ($n=14$)	Colostomy ($n=7$)	Resection ($n=5$)	Catheter jejunostomy ($n=5$)	Biopsy ($n=9$)
Symptomatic improvement	11	6	4	3	0
Improvement of oral food intake	10	4	3	0	0
Discharged home	11	4	2	0	0
Perioperative death*	1	0	0	0	2
Mean (range) survival (days)	252 (11–545)	130 (39–240)	100 (52–160)	52 (31–75)	65 (2–184)

*Within 30 days of operation

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Prolonged peripheral parenteral nutrition with an ultrafine cannula and low-osmolality feed

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Peripheral parenteral nutrition is an attractive alternative to centrally delivered parenteral nutrition because it obviates the need for central venous cannulation and its attendant complications. Some 45 consecutive patients were fed peripherally using a 22-G polyurethane catheter and a fat-based, low-osmolality feed. Of these patients, 36 were fed for a median of 8·5 (range 3–31) days without peripheral vein thrombophlebitis (PVT). Seven patients developed PVT after a median of 6 (range 5–7) days. The cumulative daily risk of PVT was 0·016 episodes per day. These results suggest that prolonged (more than 7 days) problem-free peripheral parenteral nutrition is possible.

Prolonged fasting and malnutrition adversely affect patient morbidity and mortality[1–3]. Total parenteral nutrition (TPN) through a central line has been used to reduce this excess morbidity. Most complications of TPN result directly from central venous cannulation[4–7]. The peripheral route for delivery of parenteral nutrition has many theoretical advantages. Most importantly, it obviates the need for central venous cannulation. The safety and efficacy of peripheral parenteral nutrition is now accepted[8–11] and many agree that it is a suitable alternative to centrally delivered TPN for patients who require intravenous nutritional support. Peripheral parenteral nutrition is limited, however, by the development of peripheral vein thrombophlebitis (PVT) which usually leads to cannula removal and cessation of treatment[12,13]. Cannula material[14–17], size and nature[18,19], and duration of infusion[20,21] are known to affect the development of PVT. Smaller diameter cannulas and lower osmolality solutions are associated with a lower incidence of PVT[22–24]. Prospective assessment of the use of an ultrafine catheter with a low-osmolality, fat-based nutrient solution for prolonged (more than 7 days) peripheral parenteral nutrition is described.

Patients and methods

Patients

All patients who required parenteral nutrition were considered eligible for intravenous nutrition via the peripheral route (*Table 1*). Patients referred from other centres and who had had previous central lines were considered for peripheral parenteral nutrition until radiological imaging of upper body venous anatomy allowed formal insertion of a Broviac catheter for central TPN.

Catheter

The Hydrocath Mid-Line (Viggo-Spectramed, Swindon, UK) was used in this study. It has an external diameter of 0·8 mm (22 G), an intravascular length of 200 mm and is made of polyurethane. Catheters were inserted using an aseptic Seldinger technique and sutured to the skin. Peripheral parenteral nutrition was started on the evening of catheter insertion and the nutrient fluid delivered by an infusion pump over a period of 24 h. Care of the catheter was by specialist nutrition nurses and all catheter handling was performed using an aseptic technique.

Table 1 Diagnoses of patients who required peripheral parenteral nutrition

Diagnosis	No. of patients
Upper gastrointestinal malignancy	18
Crohn's disease (including fistulas)	11
Non-Crohn's fistulas	5
Prolonged postoperative ileus	5
Pancreatitis	3
Other	3
Total	45

Nutrient solution

Two standard feeding regimens were used to deliver 6279 (R1; 650 mOsmol/kg) or 7953 (R2; 860 mOsmol/kg) kJ. Electrolyte profile was adjusted for each patient, depending on both serum and urinary electrolytes.

Monitoring

Haematological and biochemical parameters were monitored using the same protocol as for central TPN with electrolytes and full blood count being checked twice weekly and full nutritional indices weekly. Urinary and stomal or fistula electrolytes were measured according to the clinical condition. The catheter insertion site and predicted catheter-tip site (traced along the cephalic or basilic vein) were checked daily at the start of each infusion bag, and the appearance of pain, swelling, erythema or tenderness was documented. Any two of these signs were taken to indicate the development of PVT[12] and peripheral parenteral nutrition was stopped. After removal the catheter tip was sent for culture.

Statistical analysis

Data were analysed using Minitab (Minitab Ltd., Coventry, UK) to apply the Mann–Whitney *U* test.

Results

Over a 15-month period 45 patients (25 women; median age 64 (range 28–87) years, received peripheral parenteral

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nutrition using this cannula and feeding regimen. Twenty-three patients received the R1 formulation and 22 the R2.

The median duration for delivery of peripheral nutrition for the group was 7 (range 2–31) days. Thirty-six patients were fed for a median of 8·5 (range 3–31) days without evidence of PVT; peripheral parenteral nutrition was stopped only on the basis of clinical judgement and was followed by elective cannula removal. Seven patients developed clinical signs suggestive of PVT after a median of 6 (range 5–7) days and peripheral parenteral nutrition ceased after removal of the cannula. No patient suffered any untoward sequelae after cannula removal. Two patients (both elderly women with 'poor quality' veins) developed local swelling at the venotomy site as a result of extravasation of the nutritive fluid 2 and 3 days after cannula insertion and both cannulas were removed without further sequelae. Of the patients in whom peripheral parenteral nutrition stopped because of the development of PVT or extravasation, a central line was required in four for the continuation of parenteral nutrition. In the other five oral intake was resumed.

In this series, 45 patients received a total of 434 days of peripheral parenteral nutrition (mean 9·6 days per patient). The cumulative daily risk for the development of PVT was 0·016 episodes per day (seven of 434). PVT resulted in a significant reduction in the duration of peripheral parenteral nutrition ($W=920$, $P=0{\cdot}009$). There was no significant difference in age or sex between those who developed PVT and those who did not. There was no difference in the rate of PVT between those patients who received the R1 feeding regimen (three of 23) and those who received the R2 (four of 22). The cannula tip at elective removal was sterile in 13 of 17 patients, but culture of the cannula tip was positive in three of six patients with PVT ($P=0{\cdot}3$, Fisher's exact test). There were no episodes of sepsis (systemic or local) related to use of the catheter.

Discussion

A recent study found that of 100 consecutive surgical patients, 27 were undernourished[25]. Poor nutrition adversely affects surgical morbidity and attempts to rectify this have usually involved administration of TPN. The use of TPN, however, is modulated by potential mechanical and metabolic complications. Peripheral parenteral nutrition is an attractive alternative because it is cheap, simple to use and obviates the need for central venous cannulation. Its use is, however, limited by the development of PVT and also because it is perceived to be 'the poor relation of the other forms of nutrition support'[26]. Although the development of PVT is multifactorial[8], significant individual contributory factors include cannula material and size, duration of infusion[27,28], infusion osmolality and pH[29], and the nature of the infusion. These factors are comprehensively discussed in a recent review[8]. Polyurethane cannulas have lower rates of PVT when used for peripheral parenteral nutrition[16] and were chosen for the present study. Vascular endothelial damage may be chemically induced as higher osmolality solutions are associated with a greater risk of PVT[19,23]. A low-osmolality, fat-based solution was used in this study. The development of lipid emulsions for intravenous infusion has arguably been one of the most important advances in the development of TPN and the feasibility of peripheral parenteral nutrition[30,31]. Not only does lipid reduce the final osmolality of the nutrient solution but it appears to have a protective effect on venous endothelium over and above the reduction in osmolality[32–34].

Madan *et al.*[19] used a 15-cm, fine-bore silicone cannula inserted into a proximal forearm vein and administered a 2·5-litre all-in-one nutrient solution (Intralipid 20 per cent to provide 70 per cent of calories) of 1250 mOsmol/kg final osmolality and providing 7535 kJ. They also added heparin (500 units/l) and hydrocortisone (5 mg/l) to the feed as prophylaxis against PVT. Some 27 patients received a median of 5 (range 2–14) days of peripheral parenteral nutrition. PVT developed in two patients and mechanical occlusion in four. In that study 21 of 27 patients received problem-free peripheral parenteral nutrition. Kohlhardt and Smith[10] used a long (15 cm) silicone catheter and a 3-litre fat-based solution and achieved a median cannula lifespan of 9 (range 5–60) days. They obtained a phlebitis risk of 0·016 episodes per day (11 episodes in 61 cannulas). In the present study the efficacy of an ultrafine cannula made of a low thrombogenicity material delivering infusion of a low-osmolality, fat-based parenteral nutrition regimen has been demonstrated. Some 36 patients successfully received a median of 8·5 days of peripheral parenteral nutrition without evidence of PVT and a further seven received a median of 6 days nutrition before the development of PVT. No specific steps for PVT prophylaxis were required and the daily risk of the development of PVT was 0·016 episodes per day.

A recent survey of artificial nutrition support in the UK found that nearly 50 per cent of all courses of TPN were for less than 7 days[35]. It is therefore apparent that the peripheral parenteral nutrition regimen described in the present study would have been satisfactory for up to 50 per cent of such courses. This could have produced considerable financial savings, and a reduction in medical or nursing time and morbidity associated with central venous cannulation. In their original national survey of 1988 Payne-James *et al.*[36] reported that only 7 per cent of all parenteral nutrition was administered peripherally. In 1991 this number had doubled to 15 per cent. However, it is apparent that there is scope for a further increase in the use of this technique.

The safety, efficacy and desirability of peripheral parenteral nutrition is now well established and it should no longer be considered for only short-term feeding. This study confirms that recent advances in the understanding and prevention of PVT have made peripheral parenteral nutrition the preferred choice for most patients who require intravenous nutrition support. 'We have come full circle to a situation where a majority of patients can be provided with safe intravenous nutrition administered entirely through a peripheral vein'[37].

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Hepatectomy with an ultrasonic dissector for hepatocellular carcinoma

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This study compared the results of hepatectomy for hepatocellular carcinoma (HCC) using an ultrasonic dissector with those of a combination of the crushing clamp and finger fracture techniques. The crushing clamp and finger fracture method was used from 1989 to 1992 in 96 patients (group 1) and the ultrasonic dissector from 1993 to 1994 in 69 patients (group 2). Data from these two sets of patients were collected prospectively. The groups were comparable in terms of preoperative liver function, tumour size and stage, and the incidence of cirrhosis. Major hepatectomy was performed in 69 patients (72 per cent) of group 1 and in 52 (75 per cent) of those in group 2. Use of the ultrasonic dissector resulted in lower mean(s.e.m.) blood loss (group 1 3·4(0·4) litres *versus* group 2 2·4(0·2) litres, $P = 0{\cdot}02$), lower mean(s.e.m.) blood transfusion requirement (2·2(0.2) *versus* 1·2(0·2) litres, $P = 0{\cdot}001$) and more patients not requiring blood transfusion (8 per cent of group 1 *versus* 32 per cent of group 2, $P = 0{\cdot}0001$). Postoperative complications occurred in 45 patients (47 per cent) of group 1 and 19 (28 per cent) of those in group 2 ($P = 0{\cdot}012$). There were no deaths in group 2 whereas the hospital mortality rate in group 1 was 16 of 96 (17 per cent) ($P = 0{\cdot}0004$). A wider tumour-free resection margin (mean(s.e.m.) 1·2(0·1) *versus* 0·9(0·1) cm, $P < 0.05$) and lower serum bilirubin level throughout the postoperative period were also observed in group 2 patients. The ultrasonic dissector is better than the crushing clamp and finger fracture technique in hepatectomy for HCC.

The ultrasonic dissector was introduced in 1984 by Hodgson and DelGuercio[1] as an instrument for parenchymal transection during hepatectomy. The device was adopted by many surgeons[2–7] but clinical data demonstrating its superiority over other surgical techniques are not yet available. Over the past 5 years the present authors have changed their technique of parenchymal transection during hepatectomy from a combination of the crushing clamp[8] and finger fracture[9] methods to that of ultrasonic dissection. The present report compares the results of hepatectomy with the ultrasonic dissector with those of a combined crushing clamp and finger fracture technique in patients with hepatocellular carcinoma (HCC).

Patients and methods

Between April 1989 and September 1994, 165 patients with HCC underwent hepatectomy. Preoperative assessment included ultrasonography, computed tomography, hepatic arteriography, and routine haematological and biochemical tests. An indocyanine green clearance test was also performed. All data were recorded prospectively.

Surgical technique

Hepatectomy was performed through a bilateral subcostal incision with upward midline extension in all patients except seven who required thoracic extension for large right lobe tumours. Preliminary hilar dissection was performed in all patients undergoing lobar resection to control the ipsilateral branch of the portal vein and hepatic artery. The line of parenchymal transection was determined by intraoperative ultrasonography so that major hepatic veins were avoided at the transection line and an adequate margin obtained.

In the initial period (1989–1992), the crushing clamp method was used in 96 patients (group 1) to divide the liver parenchyma. The tubular structures exposed after application of the crushing clamp were treated with diathermy, ligated or clipped. At the deeper portion of the transection plane, the transection was completed by the finger fracture method. During parenchymal transection, intermittent vascular inflow occlusion for 15 min was applied with release of the clamp for 5 min between each clamping period.

In the later period of the study (1993–1994), the ultrasonic dissector was used in 69 patients (group 2) for parenchymal transection. In the first 18 patients undergoing hepatectomy with the ultrasonic dissector, intermittent vascular inflow occlusion was employed; in all subsequent patients parenchymal transection was performed without inflow occlusion. The ultrasonic dissector was applied at the proposed transection line after the liver capsule had been opened by diathermy The power output was set at 40 W for a normal liver and up to 70 W for a cirrhotic liver depending on the amount of fibrous tissue encountered. The rate of saline irrigation was set to the minimum whereas the suction pressure was set to the maximum. An additional fine aspirator was used to clear away from the tip of the ultrasonic dissector the saline injected and the tissue debris and bleeding that was generated during transection. The tip of the dissector was moved in a direction horizontal to the transection plane and the amplitude of movement kept to the minimum. Tiny tubular structures exposed were cauterized by the assistant while the surgeon continued to apply the ultrasonic dissector without interruption. Larger vessels of more than 1 mm were clipped or ligated. Bleeding from major branches of blood vessels encountered during transection was controlled temporarily with a pair of DeBakey forceps by the assistant while the surgeon continued to clear the parenchyma around the blood vessel; sutures were then passed to ligate the vessel on both sides before division.

Operative and postoperative data

Blood loss was estimated from the volume of fluid in the suction bottles and weight of gauze soaked with blood. For patients in group 2, the volume of normal saline was deducted from the total volume in the suction bottle. Blood transfusion was initiated entirely by the anaesthetist and was judged to be necessary when there was massive bleeding or when the haemoglobin level fell to 9 g/dl. There was no change in the anaesthetic technique over the study periods and epidural analgesia was not used.

Hospital mortality was defined as death within the admission for the operation. All postoperative complications that affected the postoperative course were recorded. Resected liver

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specimens were subjected to pathological examination to determine tumour node metastasis (TNM) stage[10] and width of tumour-free resection margin.

Statistical analysis

Results were expressed as mean(s.e.m.). Student's t test was used to compare continuous variables and the χ^2 test to compare discrete variables. Statistical analysis was performed with the help of the Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, USA).

Results

The two groups of patients were comparable in terms of age, preoperative haematological and biochemical data, indocyanine green clearance test and distribution of Child grade[11] (*Table 1*).

The operative procedures were similar in the two groups (*Table 2*). Major hepatectomy was performed in 69 patients (72 per cent) of group 1 and in 52 (75 per cent) of those in group 2. The duration of the operation was also similar. The mean(s.e.m.) volume of fresh frozen plasma used was lower in patients of group 2 (0·16(0·05) *versus* 0·38(0·06) litres, $P = 0·04$). The estimated volume of blood loss was lower in patients of group 2, in whom the mean volume of blood transfusion was also significantly less. The proportion of patients not requiring intraoperative blood transfusion was also significantly greater in group 2. There was a trend toward reduced blood loss and transfusion requirement as surgical experience increased through time (*Fig. 1*). In patients of

Table 1 Preoperative data

	Group 1 ($n = 96$)	Group 2 ($n = 69$)
Mean(s.e.m.) age (years)	54(1·2)	52(1·6)
Sex ratio (M:F)	84:12	57:12
Mean(s.e.m.) haemoglobin level (g/dl)	13·4(0·2)	14·0(0·2)
Mean(s.e.m.) platelet count ($\times 10^9$/l)	203(10)	206(11)
Child grade		
A	91	68
B	5	1
C	0	0
Mean(s.e.m.) ICG$_{15}$ (%)	13·5(0·8)	12·0(0·9)
Hepatitis B	79	53
Alcoholism	8	3

ICG$_{15}$, indocyanine green retention 15 min after intravenous injection

Table 2 Intraoperative data

	Group 1 ($n = 96$)	Group 2 ($n = 69$)
Operative procedure		
Right hepatic lobectomy	36	27
Right extended lobectomy	19	8
Right trisegmentectomy	5	7
Left hepatic lobectomy	4	5
Left extended lobectomy	5	5
Left lateral segmentectomy	9	5
Segmentectomy	6	9
Subsegmentectomy	12	3
Mean(s.e.m.) estimated blood loss (litres)	3·4(0·4)*	2·4(0·2)
Mean(s.e.m.) blood transfusion (litres)	2·2(0·2)†	1·2(0·2)
Mean(s.e.m.) operating time (h)	5·5(0·2)	5·7(0·2)
Patients not requiring blood transfusion		
Normal liver	2	4
Chronic active hepatitis	2	9
Cirrhosis	4	9
Total	8 (8)‡	22 (32)

*$t = 2·28$, $P = 0·024$; †$t = 3·55$, $P = 0·001$; ‡$\chi^2 = 14·73$, $P = 0·0001$ (values in parentheses are percentages). 162 d.f.

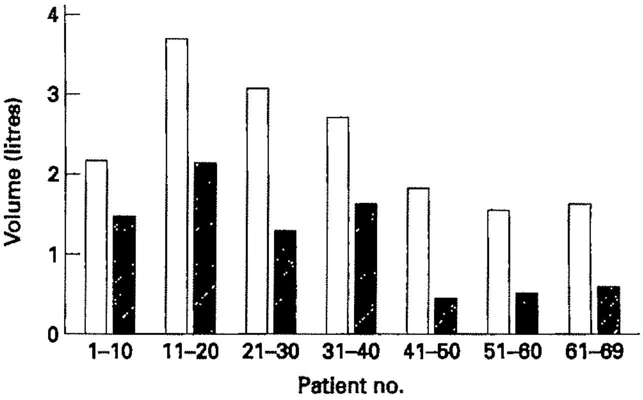

Fig. 1 Mean volume of blood loss (□) and blood transfusion (■) in sequential groups of ten patients operated on with the ultrasonic dissector

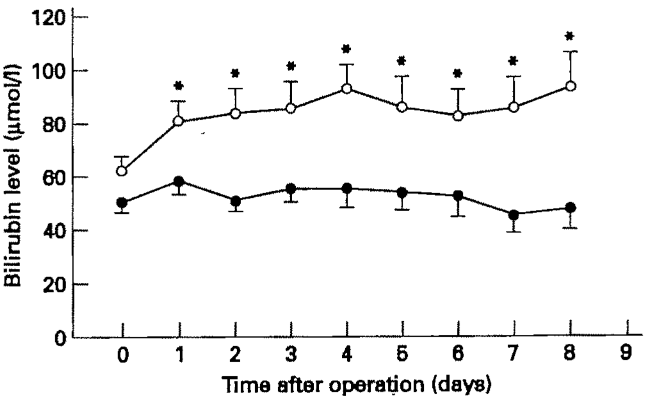

Fig. 2 Mean(s.e.m.) postoperative serum bilirubin level in patients operated on by the crushing clamp and finger fracture technique (group 1; ○) and with the ultrasonic dissector (group 2; ●). * $P < 0·05$ (Student's t test)

Table 3 Estimated blood loss and transfusion requirement in patients with different underlying liver histology

	Estimated blood loss (litres)		Blood transfusion (litres)	
	Group 1	Group 2	Group 1	Group 2
Normal liver	2·46(0·5)	1·72(0·3)	1·59(0·3)	0·85(0·2)
Chronic active hepatitis	3·6(0·7)	2·5(0·4)	2·0(0·3)	1·2(0·3)
Cirrhosis	3·7(0·6)	2·7(0·4)	2·4(0·4)*	1·3(0·3)

Values are mean(s.e.m.). *$t = 2·03$, 162 d.f., $P = 0·02$

Table 4 Pathological data

	Group 1 ($n = 96$)	Group 2 ($n = 69$)
Mean(s.e.m.) tumour size (cm)	8·9(0·5)	8·1(0·6)
Mean(s.e.m.) tumour-free margin (cm)	0·9(0·1)	1·2(0·1)*
TNM stage		
I	5	4
II	31	26
III	41	32
IVA	17	7
IVB	2	0
Associated condition		
Cirrhosis	54	30
Chronic active hepatitis	23	23

TNM, tumour node metastasis. *$t = 2·01$, 162 d.f., $P = 0·046$

Table 5 Complications and hospital mortality

	Group 1 ($n = 96$)	Group 2 ($n = 69$)
Chest infection	20 (1)	4
Pleural effusion requiring chest tapping	19	6
Wound infection	5	3
Wound dehiscence	2	0
Subphrenic abscess	6 (3)	5
Postoperative intra-abdominal bleeding	4	2
Variceal bleeding	0	1
Peptic ulcer bleeding	3	0
Urinary tract infection	1	0
Ascites requiring a diuretic	44	7
Biliary fistula	7	2
Empyema thoracis	0	1
Intestinal obstruction	0	1
Hepatic coma	9 (9)	0
Central line sepsis	1	0
Myocardial infarction	1 (1)	0
Pericardial effusion	1 (1)	0
Hospital mortality	16*	0

Each patient can have more than one complication. Values in parentheses are numbers of patients dying from the complication. *One death was from rapid intrahepatic recurrence

group 2, use of vascular inflow occlusion did not result in a difference in the volume of intraoperative blood loss.

The estimated blood loss and blood transfusion requirement were analysed according to the histology of the non-malignant part of the liver. A reduction in estimated blood loss and blood transfusion with the ultrasonic dissector was seen in all three groups of patients with different histology (normal liver, chronic active hepatitis, cirrhosis) but a significant reduction in blood transfusion requirement was seen only in those with cirrhosis (*Table 3*). In the postoperative period, the serum bilirubin level in patients of group 2 was consistently lower than that of those in group 1 (*Fig. 2*). In patients of group 2, use of vascular inflow occlusion did not result in a significant difference in postoperative serum bilirubin level.

Pathological examination of the resected specimens showed that the size of the tumours, the incidence of cirrhosis and TNM stage[10] of the two groups were comparable but that the tumour-free resection margin was significantly larger in patients of group 2 (*Table 4*).

Postoperative complications occurred in 45 patients (47 per cent) of group 1 and 19 (28 per cent) of group 2 ($P = 0·012$) (*Table 5*). Death in hospital occurred in 16 patients (17 per cent) of group 1 but in none of group 2 ($P = 0·0004$). The majority of deaths in group 1 were from massive intraoperative bleeding that led to fatal hepatic coma.

Discussion

In the past four decades the technique of parenchymal transection during hepatectomy has evolved from the use of closed scissors and scalpel handle[12] to finger fracture[9] and use of a crushing clamp[8] (as a miniature of the finger fracture technique), and finally to the use of ultrasonic and waterjet dissectors[13]. The present report demonstrates that the ultrasonic dissector appears to be better than use of a crushing clamp and finger fracture in terms of blood loss and transfusion requirement, postoperative morbidity and mortality, tumour-free resection margin and postoperative serum bilirubin level. This improvement in results could be due to the increasing experience gained by the authors over these years but they believe that the ultrasonic dissector is a major factor.

The mean blood loss in this series was higher than in some recent reports[14]. This is because the majority of procedures were major hepatectomy for large tumours and nearly 80 per cent of patients had underlying chronic liver disease (*Table 4*). Bleeding can occur in many places during major hepatectomy but bleeding from the branches of the hepatic vein at the time of parenchymal transection is usual. It was found that with use of the ultrasonic dissector, the localization and control of the branches of the hepatic vein was more efficient than when using the crushing clamp and finger fracture method.

The ultrasonic dissector also allows precise division of the liver along the plane determined by intraoperative ultrasonography. Division of the liver by the crushing clamp can also be very precise but is possible only at the superficial portion of the transection plane. Application of the crushing clamp method becomes increasingly difficult on approaching the deeper portion of the transection plane. The finger fracture technique can be advantageous at the deep portion of the transection plane, but only when separation of the posterior surface of the liver from the inferior vena cava has been completed. The finger fracture method, however, is never precise. In patients with a large tumour the transection plane frequently goes into the space between the tumour capsule and the uninvolved liver, rendering the tumour-free resection margin unsatisfactory.

Parenchymal transection with the ultrasonic dissector is not entirely bloodless. Bleeding will occur when the power output is set excessively high so that larger blood vessels are divided. Excessive bleeding from the transected area can also occur when the surgeon is anxious to proceed quickly by applying the tip of the ultrasonic dissector over a wide amplitude. This occurred in the present authors' early experience. In this situation bleeding from the transected area can be so diffuse that the assistant does not have a chance to stop it. Slow and cautious movement of the tip, and a power output that did not induce excessive bleeding, were thus used. As a result, the time required for completion of parenchymal transection was much prolonged. However, the total time of the operation was not significantly longer than when the crushing clamp and finger fracture technique was employed. This was because the transection surface left after the crushing clamp and finger fracture technique often oozed profusely and much time was required for haemostasis whereas the transection surface left after use of the ultrasonic dissector was often completely dry.

In patients with cirrhosis and chronic active hepatitis, it was found that the ultrasonic dissector was equally effective as in those with a normal liver. Indeed patients with cirrhosis distinctly benefited in terms of blood transfusion requirement. The power output had to be set at a higher level for the amount of fibrous tissue present but the clarity of the field was similar to that of normal liver.

In conclusion, use of the ultrasonic dissector is preferred in hepatectomy for HCC because it was associated with less blood loss, a larger tumour-free resection margin, lower postoperative serum bilirubin level, fewer postoperative complications and no hospital mortality. Since this study was a retrospective comparison, a prospective randomized trial between finger fracture and the ultrasonic dissector would be needed to prove definitely the superiority of the latter.

Acknowledgements

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Effects and limitations of prolonged intermittent ischaemia for hepatic resection of the cirrhotic liver

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Intermittent clamping of the hepatic pedicle during hepatectomy may reduce operative bleeding, but its limitations and long-term effects on the cirrhotic liver are unknown. Eighty-three patients with cirrhosis undergoing hepatectomy with repeated clamping for 15 min and declamping for 5 min were divided into three groups based on total clamping duration: group 1 less than 40 min (39 patients); group 2 40–80 min (28); group 3 more than 80 min (16). Larger tumours were associated with longer ischaemia times ($P = 0.002$), longer operating times, greater operative blood loss and increased blood transfusion requirements ($P < 0.001$), and resulted in higher postoperative levels of serum transaminases and lactic dehydrogenase ($P < 0.001$). Operative morbidity and mortality rates, and the late hepatic failure rate, were not affected. The longest total ischaemia time was 204 min but the uppermost time limit for hepatic ischaemia remains to be determined.

The control of bleeding during liver resection remains a major technical challenge[1–5]. Early this century Pringle[6] completely clamped off the inflow of blood to arrest bleeding after liver trauma and many surgeons have adopted this technique to reduce operative bleeding during hepatic resection[2–5]. A normal liver can tolerate a warm ischaemia time of more than 60 min[3–7].

Although the cirrhotic liver is unable to tolerate ischaemia as well as a normal liver[2,3,8], several surgeons have advocated the use of Pringle's manoeuvre to reduce bleeding during resection of a cirrhotic liver[2,9–15]. A safe upper time limit for a cirrhotic liver of 75 min of continuous ischaemia has recently been reported[14], but this limit requires re-evaluation because of the limited number of patients in that study and the contradictory results of others[3,12].

Intermittent clamping may increase the total ischaemia time for hepatectomy[2,6,11,13] to 90 min, but the maximum time and the effects of this technique remain unclear.

This technique[16] has been used in the authors' department since 1989, and this study examined the results to determine its long-term effects and limitations in patients with cirrhosis.

Patients and methods

The surgical results of 83 patients with histologically proven cirrhosis undergoing hepatic resection for liver cancer were reviewed. Patients with no cirrhosis and those with cirrhosis who did not require this technique were excluded. The tumours were hepatocellular carcinoma (HCC) in 79 patients, cholangiocarcinoma in two, inflammatory pseudotumour in one and metastatic colonic cancer in one. The aetiology of the cirrhosis was posthepatitic in 80 patients and alcoholic in three.

Before operation serum levels of hepatitis B surface antigen (HBsAg), liver function and indocyanine green (ICG) clearance were assessed. Upper gastrointestinal endoscopy and imaging studies (including abdominal ultrasonography, computed tomography and angiography) were performed on each patient. All patients were graded for prognosis using the Child classification[17].

The indications for surgery in these patients were as reported previously[16]. In patients with cirrhosis only those without ascites, with a serum total bilirubin concentration of less than 3·5 mg/dl and ICG 15-min retention rate of less than 40 per cent were selected for resection. To preserve as much liver tissue as possible[18] the extent of hepatectomy was determined by the ICG clearance rate and the modified criteria of Makuuchi *et al.*[9].

At operation the hepatic parenchyma was crushed and transected with a Kelly clamp[18]. Intermittent cross-clamping of the portal triad was performed using a Satinsky vascular clamp. Hydrocortisone 100 mg was infused before clamping[9], which was continued for 15 min and discontinued for 5 min. The transection was stopped temporarily and bimanual compression of the resection plane performed to achieve temporary haemostasis, during the declamping period. Clamping was repeated until the tumour was completely excised and all areas of bleeding had been arrested. Any adjacent organs invaded by the tumour were concomitantly resected.

After operation serum levels of total bilirubin and liver enzymes, including serum glutamic–oxaloacetic transaminase (SGOT), serum glutamic–pyruvic transaminase (SGPT) and lactic dehydrogenase (LDH), were measured on days 1, 3, 5 and 7 after operation.

Based on previous reports on the maximum duration of warm ischaemia of the cirrhotic liver[10,14] and the total duration of inflow vascular clamping, patients were divided into three groups: (1) total ischaemia time less than 40 (range 9·5–36) min ($n = 39$); (2) total ischaemia time 40–80 min ($n = 28$); and (3) total ischaemia time greater than 80 (range 84–204) min ($n = 16$).

Complications or deaths that occurred during the postoperative period, or within 30 days of operation, were defined as operative morbidity and mortality.

Continuous variables are presented as mean(s.d.). Statistical comparisons of the three groups were performed using the χ^2 test and one-way analysis of variance (ANOVA). $P < 0.05$ was considered to be statistically significant. All surviving patients were followed until December 1994. The Kaplan–Meier method was used to estimate the disease-free and actuarial survival rates.

Results

Clinical details and operating procedures

The mean(s.d.) total hepatic ischaemia times for patients in groups 1, 2 and 3 were 25·5(6·7), 58·3(10·2) and 110·5(34·7) min respectively. The longest duration in this series was 204 min for three separate resections in a patient with multiple tumours over both lobes. No haemodynamic changes were seen during the clamping or

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declamping periods. In 17 patients concomitant resection of adjacent organs was performed (diaphragm in 11, pancreas in two, stomach in two, colon in two, spleen in two, bile duct in one and main portal vein in one).

Table 1 Clinical details and surgical procedures in patients with cirrhosis who underwent intermittent hepatic inflow occlusion during liver resection

	Group 1 ($n=39$)	Group 2 ($n=28$)	Group 3 ($n=16$)	P
Sex ratio (M:F)	33:6	21:7	11·5	0·38‡
Age (years)*	56·4(11·6)	57·3(10·2)	53·6(12 8)	0·55§
Child grade				
A	30	23	15	0·11‡
B	8	5	0	
C	1	0	1	
HBsAg positive	32	20	15	0·19‡
Associated oesophageal varices	7	3	1	0·45‡
Tumour size (cm)*	5·8(3·9)	7·7(3·8)	9·5(5·1)	0·002§
ICG R-15 (%)*	14·5(6·1)	14·2(6·0)	13·9(6·4)	0·91§
Serum albumin (g/dl)*	3·82(0·61)	3·89(0·53)	4 10(0·50)	0·17§
Serum bilirubin (mg/dl)*	1·10(0·59)	0·85(0·34)	1 01(0·55)	0·54§
Prothrombin time (% of normal control)*	93·6(5·8)	94·6(5·4)	96·8(3·3)	0 11§
Liver resection†				
≥3 segments	2	8	4	0·09‡
2 segments	17	8	4	
≤1 segment	20	12	8	
Concomitant resection of adjacent organs	4	7	6	0·06‡

*Values are mean(s.d.). HBsAg, hepatitis B surface antigen; ICG R-15, indocyanine green 15-min retention rate. †The extent of liver resection was according to Couinaud's definition[1,5,9,18]. ‡χ^2 test; §one-way analysis of variance

As shown in *Table 1* the only significant difference in patient details was tumour size. Larger tumours usually required longer ischaemia times because more complicated hepatectomy procedures were necessary. A slightly higher incidence in combined resection of adjacent organs ($P=0·06$) and wider extent of hepatectomy ($P=0·09$) were associated with a longer ischaemia time.

Early postoperative results

Mean(s.d.) operating times for groups 1, 2 and 3 were 238·2(92·4), 340·5(118·4) and 397·2(119·1) min respectively

Table 2 Postoperative complications of patients with cirrhosis who underwent intermittent hepatic inflow occlusion

	Group 1 ($n=39$)	Group 2 ($n=28$)	Group 3 ($n=16$)
No. of patients with complications	7	3	4
Bile leakage	0	0	3
Upper gastrointestinal bleeding	1*	0	1
Pancreatic fistula	1	0	0
Anaesthetic accident	1*	0	0
Pleural effusion	0	2	1
Abdominal abscess	1	0	0
Wound infection	0	1	0
Prolonged jaundice†	1	1	2
Ascites	1	0	2
Death	2	0	0

*Caused operative death; †defined as serum total bilirubin level of 5 mg/dl or greater for 7 days

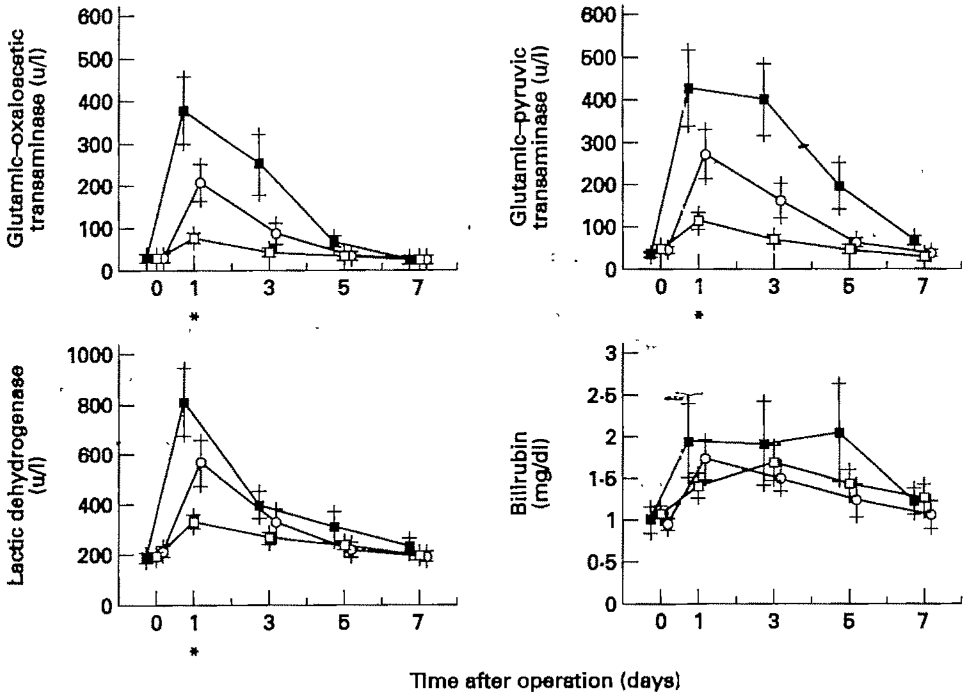

Fig. 1 Changes in the concentration of liver enzymes and serum bilirubin after intermittent hepatic inflow occlusion in patients with cirrhosis. Values are mean(s.e.m.). A value of zero for the postoperative day refers to the preoperative value. □, Group 1 ($n=39$); ○, group 2 ($n=28$); ■, group 3 ($n=16$). *F ratio > 11·0; 2, 80 d.f., $P<0·001$ (group 1 *versus* group 2 *versus* group 3, one-way analysis of variance)

(F ratio = 15·08; 2, 80 d.f., $P<0{\cdot}001$). Mean(s.d.) operative blood loss and blood transfusion volumes for groups 1, 2 and 3 were 450·8(334·6), 1334·5(1072·1) and 1622·5(1046·6) ml (F ratio = 16·69; 2, 80 d.f., $P<0{\cdot}001$) and 108·9(383·9), 602·8(762·8) and 805·9(654·8) ml (F ratio = 10·93; 2, 80 d.f., $P<0{\cdot}001$) respectively.

Peak SGOT, SGPT and LDH levels occurred on the first postoperative day and gradually returned to preoperative levels after 1 week. Serum total bilirubin concentration was raised on the first postoperative day and decreased to preoperative levels after 1 week (*Fig. 1*). The longer the total ischaemia time, the higher the increase in SGOT, SGPT and LDH levels. However, this trend was not observed for serum bilirubin.

Postoperative complications occurred in 14 patients (17 per cent) (*Table 2*). There were no significant differences between the three groups and no patient required reoperation. Two patients in group 1 with HCC died 35 and 48 days after operation.

Long-term results

One patient in group 1 and another in group 3 died from late hepatic failure, without tumour recurrence, 38 and 49 months after operation. One patient with HCC in group 1 underwent a concomitant gastrectomy at the time of hepatectomy and died from disseminated disease 8 months after operation. At the time of this report 51 patients were alive and 48 were tumour free. The major cause of death was recurrent cancer. For patients with malignant tumour the 3-year disease-free survival rate and the actuarial survival rates were 46 and 59 per cent respectively.

Discussion

Application of compressing liver clamps is difficult for the resection of a centrally located tumour[2,16] and temporary clamping of the hepatic pedicle (Pringle[6]) is a quick and simple manoeuvre for reducing operative bleeding[2–5,9–15]. Prolonged occlusion causes intestinal congestion, liver cell anoxia and even death[2,7]. Huguet *et al.*[3] reported a safe upper time limit of over 60 min for a normal liver, and recently it has been shown[4,5] that a normal liver can withstand continuous warm ischaemia for periods exceeding 2 h.

The cirrhotic liver may be more vulnerable to massive haemorrhage and ischaemic injury than a normal liver[2,3,8,15], although others have reported that a compensated cirrhotic liver can tolerate warm ischaemia[2,10–15]. By continuous inflow occlusion Nagasue *et al.*[10] reduced the operative bleeding and mortality rates for resection of the cirrhotic liver, with a longest duration of occlusion of 32 min. Kim and co-workers[14] reported that 'early-stage' cirrhotic livers can withstand continuous hepatic inflow occlusion for 75 min. In contrast, Huguet *et al.*[3] reported that even with an occlusion time of less than 50 min three of five patients with cirrhosis died. Yamaoka and colleagues[12], using a combination of venovenous bypass and total vascular exclusion, reported a time limit of 60 min for continuous hepatic pedicle clamping of a cirrhotic liver.

Owing to the poor regenerative power of the cirrhotic liver, meticulous division and ligation of intrahepatic vessels in a bloodless operating field is required to prevent ischaemic or congestive injury to the remaining liver[13,15,16,18]. As in patients in group 1 in the present study and in other reports[9–11,14], resection of a small part of the liver can be easily achieved with short periods of cross-clamping. Clamping duration of 60–75 min may be insufficient, however, for some complicated hepatectomies.

The results of this study reveal that, if the remaining liver parenchyma can be well preserved, prolonged intermittent ischaemia does not increase operative morbidity or mortality rates, and does not have long-term sequelae. The long-term results were comparable to those in other reports[9,15,18]. Late liver failure in two patients could not be attributed to prolonged ischaemia time, as both deaths occurred more than 3 years after hepatectomy. Selected cirrhotic livers can therefore withstand prolonged intermittent ischaemia for over 200 min, a period within which any difficult hepatectomy can be safely accomplished.

Although this study did not allow definition of the uppermost time limit for intermittent ischaemia in patients with a cirrhotic liver, the longer the total duration of ischaemia, the greater was the increase in serum levels of liver enzymes. Prolonged ischaemia may therefore result in more liver cell destruction. Although no patient in group 2 or 3 died, an unlimited intermittent ischaemia duration cannot be assumed. The safe upper limit for this technique, performed on the cirrhotic liver, remains to be determined.

Acknowledgements

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Short note

Effect of a low-fat, low-protein, high-carbohydrate diet on gallstone formation in the hamster

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Many epidemiological studies support the assumption that diet is of great importance in the pathogenesis of cholesterol gallstones[1], but its role in the origin and development of non-cholesterol gallstones is less clear. In humans, a low-fat, low-protein, high-carbohydrate diet seems to increase the development of pigment gallstones[2]. The purpose of this study was to explore therefore the effect of a low-fat, low-protein, high-carbohydrate diet on the formation of gallstones and their composition. Hamsters were used because gallstones induced in these animals can be either cholesterol or pigment, depending on dietary constituents[3].

Materials and methods

Animal design

Syrian male golden hamsters ($n = 34$), weighing approximately 100 g, were randomized to be fed a control diet ($n = 15$) or a specially prepared diet (low fat, low protein, high carbohydrate) ($n = 19$). The animals were killed 4 months after starting the diets. The gallbladders were removed and examined for the presence of gallstones. Bile in the gallbladder was sent for bacteriological study.

Diets

The control diet (Gold Coin Mills, Singapore) comprised 2·35 per cent fat, 25·09 per cent protein and 50·15 per cent carbohydrate and was made by mixing wheat meal (36·1 per cent) with soyabean (23·5 per cent), maize (10·0 per cent), fish (7·0 per cent), wheat pollard (6·9 per cent), milk powder (6·0 per cent), tapioca (3·0 per cent), meat/bone (2·8 per cent), alfalfa (2·0 per cent), minerals (1·2 per cent), multivitamin (1·0 per cent) and palm oil (0·5 per cent). The specially prepared diet comprised 0·35 per cent fat, 4·79 per cent protein and 82·30 per cent carbohydrate, and was a mixture of rice flour (68 per cent), potato starch (22 per cent), corn starch (8 per cent), multivitamin (1 per cent) and minerals (1 per cent). Quantitative analysis of the constituents of the control and specially prepared diets is shown in *Table 1*.

Components of gallstones were qualitatively analysed by an established method using an infrared spectrophotometer (model A3; Japan Spectrophotometric, Tokyo, Japan)[4].

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Results

Gallstone formation and bacteriological study

No death or illness occurred during the experiment. Gallstones were found in the gallbladders of 11 of 19 hamsters fed a specially prepared diet, while none was found in the controls ($\chi^2 = 3{\cdot}4$, $P < 0{\cdot}001$). Bacteriological study of bile taken from the gallbladder was negative in all animals.

Components of gallstones

The main constituent of the 11 stones was calcium carbapatite (calcium carbonate and calcium phosphate). Calcium bilirubinate was found in three stones and cholesterol in one.

Discussion

The results of this study confirm the influence of diet on the formation of gallstones. The finding that the main components of stones are calcium carbapatite and calcium bilirubinate indicates that a low-fat, low-protein, high-carbohydrate diet promotes the formation of black pigment gallstones in this hamster model. The 'negative' bacteriological study of bile in the gallbladder supports a previous report that black pigment stones precipitate in sterile bile[2].

Data from this experimental hamster model can be only of tentative relevance to humans; however, the results seem to correlate with clinical findings. Analysis of stones taken from the gallbladders of more than 900 Thai patients showed that the major components are calcium bilirubinate, calcium carbonate and phosphate. Pure cholesterol stones were found in only 14 per cent[5]. The present study might explain these clinical findings as most Thai foods are high in carbohydrate, and low in fat and protein.

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Table 1 Quantitative analysis of the constituents of control and low-fat, low-protein, high-carbohydrate diets

	Moisture (%)	Crude protein (%)	Crude fat (%)	Crude fibre (%)	Ash (%)	Nitrogen-free extract (%)	Calcium (mg/100 g)	Phosphorus (mg/100 g)
Control diet	11·20	25·09	2·35	3·68	7·51	50·15	1418·29	805·59
Low-fat, low-protein, high-carbohydrate diet	11·60	4·79	0·35	0·01	0·95	82·30	220·12	83·65

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Corrigendum

H. Friess, H. G. Beger, U. Sulkowski, H. Becker, B. Hofbauer, H.-J. Dennler and M. W. Büchler. Randomized controlled multicentre study of the prevention of complications by octreotide in patients undergoing surgery for chronic pancreatitis. *British Journal of Surgery* 1995; 82: 1270–1273.

Abstract The antepenultimate sentence should read 'The overall mortality rate was 1·2 per cent (octreotide group 1·6 per cent, placebo group 0·8 per cent; *P* not significant'.

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Repeat hepatectomy for recurrent hepatocellular carcinoma

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This study evaluated the results of repeat hepatectomy for recurrent hepatocellular carcinoma (HCC) and delineated the limitations of such a treatment strategy. Of 290 patients who had radical hepatic resection, 167 had intrahepatic tumour recurrence. Fifty patients underwent a second hepatectomy. Third and fourth hepatectomies were carried out on six and two patients respectively. There were 36 men and 14 women. Age ranged from 32 to 77 years (mean 59·1 years). Liver cirrhosis was present in 38 and chronic hepatitis in 12 patients. Operative death occurred in four patients (8 per cent) after a second and in one of six after a third hepatectomy, compared with 4·5 per cent after first hepatectomy. The five postoperative deaths were attributed to either Child grade B or C liver disease, or severe intraoperative bleeding. The 5-year survival rate was better in these 50 patients (41 per cent) than in 117 patients who were treated otherwise (7 per cent). The present study indicates that repeat hepatectomy may be useful for recurrent HCC. It is indicated principally for patients with a solitary tumour and Child grade A liver disease.

Although hepatic resection is an established method of treatment for hepatocellular carcinoma (HCC), the incidence of intrahepatic recurrence is extremely high probably because of early spread of tumours, metachronous multicentric carcinogenesis and persistence of the causative factors[1–5]. Liver transplantation is indicated for patients with early stage HCC associated with advanced cirrhosis[6,7] but in Japan, where cadaveric organ donation is not feasible, hepatic resection is performed even in patients who are good candidates for liver transplantation. These circumstances have led to the performance of repeat hepatectomy for recurrent HCC in disadvantageous conditions.

In this study, the authors have retrospectively evaluated the outcome of 50 patients who underwent repeat hepatectomy for recurrent HCC, from a total of 290 patients who had primary resection during the past 14 years, to elucidate the limitations of such a treatment strategy.

Materials and methods

During the 14 years from 1980 to 1993, the senior author (N.N.) performed 290 radical hepatic resections for primary HCC at hospitals in Hiroshima (from January 1980 to March 1986) and Izumo (from April 1986 to December 1993). Repeat hepatectomy was performed in 50 patients for the treatment of intrahepatic tumour recurrence.

Patient characteristics

Initial clinical data of these 50 patients are shown in *Table 1*. HCC and associated liver disease were diagnosed histopathologically in all cases. The maximal diameter of the largest nodule was taken as the tumour size in patients with multiple tumours. Twenty-nine patients were randomized to receive chemotherapy with doxorubicin, epirubicin and/or 5-fluorouracil following the first hepatic resection.

Table 1 Clinical data at initial operation in 50 patients who had repeat hepatectomy

	No of patients
Age (mean(s.d.) 59(9) years)	
<50 years	6
50–65 years	31
>65 years	13
Sex	
Male	36
Female	14
Alcohol abuse	
Yes	20
No	30
HBs-antigen	
Positive	13
Negative	37
HCV-antibody ($n=25$)	
Positive	16
Negative	9
Underlying liver disease	
Liver cirrhosis	38
Chronic hepatitis	12
Child grade	
A	37
B	12
C	1
Tumour size	
<2 cm	5
2–5 cm	34
>5 cm	11
Postoperative chemotherapy	
Yes	29
No	21

HBs, hepatitis B surface; HCV, hepatitis C virus

Pattern of recurrence and indication for repeat hepatectomy

After the hepatectomy, 266 patients were discharged from hospital. Intrahepatic recurrence of the tumour developed in 167 (62·8 per cent) of them (*Table 2*). Of these, 82 had multiple or diffuse recurrence in the entire liver. Twenty patients with marginal or distant intrahepatic recurrence of nodular tumour(s) were excluded from repeat resection because of extrahepatic recurrence or poor hepatic function. A second hepatectomy was

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indicated in 65 patients (38·9 per cent) from both anatomical and functional viewpoints. As 15 patients refused the operation, 50 patients underwent a second hepatectomy. Based on the same criteria, a third hepatectomy was carried out on six patients and a fourth hepatectomy was performed in two (*Table 2*).

Operative procedures

The methods of hepatic resection used are shown in *Table 3*. At the first hepatectomy, several concomitant operations were carried out: distal splenorenal shunt (two patients), devascularization of the stomach with splenectomy (two) and cholecystectomy for gallstones (two). At the second hepatectomy, splenectomy was performed in four patients because of severe hypersplenism and a Warren shunt in one for oesophageal varices. Cholecystectomy was performed for gallstones in two patients.

Postoperative follow-up

After discharge from the hospital, the patients were followed up at 2-week intervals in the first 6–12 months and monthly thereafter. Serum levels of α-fetoprotein and a protein induced by vitamin K antagonist-II (PIVKA-II) were measured serially. Imaging diagnosis with ultrasonography and/or computed tomography was repeated every 3 months. When intrahepatic recurrence of the tumour was suspected, the patient was hospitalized for angiography and treatment.

Statistical analysis

Statistical comparisons for significance were made with the χ^2 and unpaired Student's *t* tests. Cumulative survival and intrahepatic recurrence rates from the first operation and after the last operation were obtained by the Kaplan–Meier method and were compared by the log rank test. P values of less than 0·05 were considered statistically significant.

Results

Child grade

The Child grade had deteriorated in three patients at the time of the second hepatectomy (*Table 4*). A third hepatectomy was performed in five patients with grade A and one patient with grade B cirrhosis but both patients who had a fourth hepatectomy had Child grade A disease.

Blood loss and operating time

Blood loss during surgery and operating time were not significantly increased at repeat hepatectomy (first *versus* third, $0{\cdot}05 < P < 0{\cdot}1$) (*Table 4*).

Tumour size and number

The incidence of tumours smaller than 2 cm was higher at second hepatectomy than at first operation ($P < 0{\cdot}05$). Multiple tumours tended to be more common at the second hepatic resection than at the first operation ($0{\cdot}05 < P < 0{\cdot}1$) (*Table 5*).

Type and time of intrahepatic recurrence

Following the first hepatectomy, 44 patients had between one and three nodular recurrences in a segment or lobe

Table 2 Intrahepatic recurrence pattern and indication for repeat hepatectomy

	Intrahepatic recurrence		
	After first operation ($n = 167$)	After second operation ($n = 35$)	After third operation ($n = 5$)
Anatomically irresectable recurrence*			
Multiple	72	17	1
Diffuse	10	1	0
Anatomically resectable recurrence†			
Repeat hepatectomy not indicated			
Simultaneous extrahepatic recurrence	7	5	2
Poor liver function	13	2	0
Repeat hepatectomy indicated			
Refused	15	2	0
Performed	50	6	2
Failed	0	2	0

*Multiple or diffuse recurrence in the entire liver; †marginal or distant intrahepatic recurrence of nodular tumour(s)

Table 3 Operative procedures in 50 patients who had repeat hepatectomy

	Hepatic resection			
Procedure	First	Second	Third	Fourth
Extended right lobectomy	1	1	0	1
Right lobectomy	7	0	1	0
Left lateral segmentectomy	2	3	0	0
Two segmentectomy*	1	1	1	0
One segmentectomy plus wedge resection	3	1	0	0
One segmentectomy	10	3	0	1
Two wedge resections	2	9	0	0
One wedge resection	24	32	4	0
Total	50	50	6	2

*Segments proposed by Couinaud

Table 4 Child grade, blood loss during surgery, and operating time in 50 patients who had repeat hepatectomy

	Child grade				
Hepatic resection	A	B	C	Blood loss during surgery (ml)*	Operating time (min)*
First ($n = 50$)	37	12	1	662(526)	120(45)
Second ($n = 50$)	34	14	2	930(753)	136(47)
Third ($n = 6$)	5	1	0	1107(886)	156(37)
Fourth ($n = 2$)	2	0	0	250, 1720	60, 250

*Values are mean(s.d.)

Table 5 Size and number of tumours in 50 patients who had repeat hepatectomy

	Tumour size (cm)			No. of tumours	
Hepatic resection	<2	2–5	>5	Solitary	Multiple
First ($n = 50$)	5	34	11	42	8
Second ($n = 50$)	13	32	5	35	15
Third ($n = 6$)	1	5	0	5	1
Fourth ($n = 2$)	1	1	0	1	1

different from the primary site. Nine had marginal recurrence at the site adjacent to the previous hepatic resection of whom three also had distant nodules. At third hepatectomy, three patients had marginal and another three had distant intrahepatic recurrence. The mean(s.d.) interval between the first and second hepatectomy was 21(14) months and that between the second and third hepatectomy was 17(14) months.

Table 6 Postoperative morbidity and mortality in 50 patients after repeat hepatectomy

	No. of patients	Postoperative complications	Operative death (within 1 month)	Overall deaths in hospital
Overall patients				
First hepatectomy	290	56 (19)	13 (4)	24 (8)
Present series				
First hepatectomy	50	5 (10)	0 (0)	0 (0)
Second hepatectomy	50	8 (16)	4 (8)*	4 (8)
Third hepatectomy	6	1 (17)	1 (17)†	1 (17)
Fourth hepatectomy	2	0 (0)	0 (0)	0 (0)

Values in parentheses are percentages. *Child grade A in one, B in two and C in one; †Child grade A but with blood loss of 3050 ml

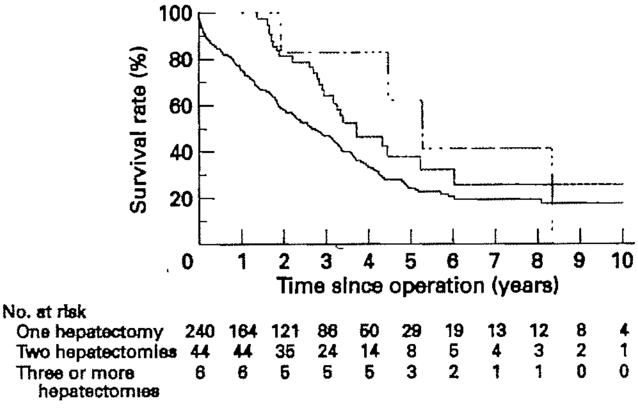


Fig. 1 Cumulative survival rates after the first hepatectomy in patients who had one (——), two (– – –) or more than two (·····) hepatectomies. There was a significant difference between patients who had one hepatectomy and those who had two hepatectomies ($P = 0.0234$), Log rank test

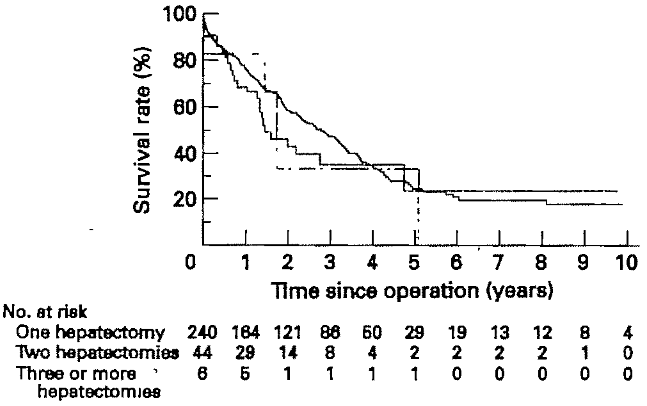


Fig. 2 Cumulative survival rates after the last hepatectomy in patients who had one (——), two (– – –) or more than two (······) hepatectomies. There were no significant differences between the three groups

Postoperative morbidity and mortality

Postoperative complications were encountered in 56 of 290 patients (19·3 per cent) after the first hepatectomy. Similar rates were obtained following repeat hepatectomy. Operative and in-hospital death rates were not significantly increased by repeat hepatectomy (*Table 6*). Overall, five deaths occurred after second or third hepatectomy; these were attributed to either Child grade B or C disease or severe intraoperative bleeding. There were ten patients with Child grade B or C disease of the 46 survivors compared with three of four patients who died after second hepatectomy ($\chi^2 = 2{\cdot}746$, 1 d.f., $P = 0{\cdot}098$). The cause of death after second hepatectomy was hepatic failure (three patients) and heart failure (one). One death after a third hepatectomy was due to coagulopathy followed by multiorgan failure. Two patients in whom a third hepatectomy had been attempted without success both died of hepatic failure within 1 month.

Survival rates

Of 290 patients who underwent radical hepatic resection, 240 had only one operation, 44 had two operations and six underwent hepatectomy three or four times. The cumulative survival rates after the first resection including operative deaths in these three groups were 47·1, 64·1 and 83·3 per cent respectively at 3 years and 24·9, 37·8 and 62·5 per cent respectively at 5 years (*Fig. 1*). There was a significant difference between patients who had one hepatectomy and those who had a second resection ($P = 0{\cdot}0234$). *Fig. 2* shows the cumulative survival rates in the same groups after the final hepatic resection. There were no differences between the groups. Of 167 patients who had intrahepatic tumour recurrence after the initial operation, 50 patients who had repeat hepatectomy had a significantly better survival rate compared with 117 patients who had palliative or no treatment ($P < 0{\cdot}0001$) (*Fig. 3*).

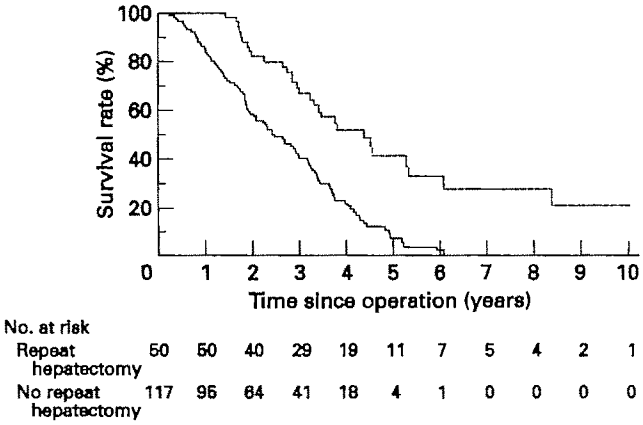
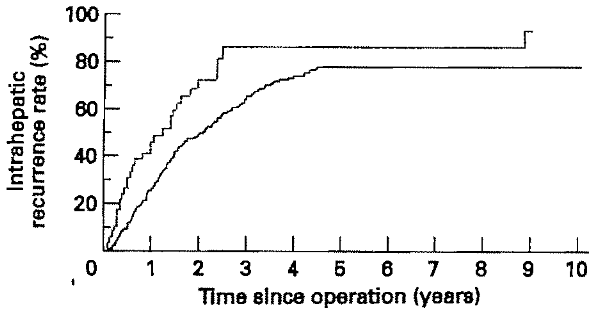


Fig. 3 Cumulative survival rates after the first hepatectomy in 167 patients with intrahepatic recurrence. The survival rate was significantly better in patients who had repeat hepatectomy (– – –) than in those who did not (——) ($P < 0{\cdot}0001$), Log rank test



No. at risk	0	1	2	3	4	5	6	7	8	9	10
After first hepatectomy	258	175	106	65	37	26	18	14	12	8	5
After second hepatectomy	46	21	8	3	2	2	2	2	2	0	0

Fig. 4 Cumulative intrahepatic recurrence rates after the first (——) and second (---) hepatectomy. The difference was not significant ($P = 0{\cdot}1742$). Operative and in-hospital deaths were excluded. Log rank test

Intrahepatic recurrence rates

Excluding in-hospital deaths, there was no significant difference in the cumulative intrahepatic recurrence rate between 266 patients after one hepatectomy and 46 patients after a second hepatectomy (*Fig. 4*) ($P = 0{\cdot}1742$).

Cause of death and patient survival

Of the 50 patients who had repeat hepatectomy, 28 died. The causes of death were operative death (five patients) hepatic failure (three), gastrointestinal bleeding (one), and cancer recurrence (19). The sites of recurrence were liver only in ten patients, liver and bone in four, liver and lung in two, generalized in two and lung only in one. At present, 22 patients are alive, 11 of whom are free from cancer and 11 with cancer (liver only in eight and liver and lung in three).

Discussion

In 1986 the authors' preliminary experience of repeat hepatectomy for recurrent HCC was reported[8]. In the same year Lee *et al.*[19] in Taiwan also stressed the value of this method in the treatment of HCC. Since then several Eastern[10–16] and Western groups[17,18] have reported similar results.

It was found in 1990 on further analysis of the data that repeat hepatectomy for recurrent HCC was associated with a better survival rate than transcatheter chemoembolization of the hepatic artery or intra-arterial infusion chemotherapy[10]. However, the 5-year survival rate in patients who had repeat hepatectomy was only 26·8 per cent even though the patients were strictly selected in terms of the tumour condition and hepatic functional reserve. The authors then began to feel that the value of repeat hepatectomy should not be exaggerated, and that introduction of more effective chemotherapy and liver transplantation should be considered.

On the other hand, other Asian authors have reported no operative mortality and a higher 5-year survival rate of 42–87 per cent after the initial hepatectomy (*Table 7*). These reports may indicate that with strict patient selection and sophisticated peroperative management, repeat hepatectomy can be performed safely with satisfactory survival rates.

The expected natural history of a patient with a true recurrence, that is persistence of the same tumour after treatment, should be different from that of a patient with multifocal disease who develops new tumour(s) at a distance. However, many of the present patients had distant tumour nodules in the liver.

The apparently increasing mortality rate of repeated resection could be attributed to deterioration of Child grade, increased incidence of multiple tumours, and the prolonged operating time and increased blood loss resulting from severe adhesions caused by previous operations. In fact, among four patients who died after a second hepatectomy, three had Child grade B or C cirrhosis. Overall, five postoperative deaths after repeat hepatic resection and two deaths after an unsuccessful third operation were ascribed to either poor functional reserve (Child grade B or C disease) or severe intraoperative bleeding. In view of these results, patients with Child grade B and C cirrhosis and those in whom severe intraoperative bleeding is anticipated are now considered to be unsuitable for repeat hepatectomy.

Of 167 patients with recurrence, the 5-year survival rate including operative deaths was significantly better in 50 patients who had repeat hepatectomy (40·9 per cent) than in 117 patients who did not (7·0 per cent). However, this does not simply mean that repeat hepatectomy is better than other methods because most candidates for repeat hepatectomy had better prognostic indicators in terms of both the tumour and hepatic function. Nevertheless, repeat hepatectomy seems to have a role in the management of these patients, but the tendency to multiple recurrence and shorter recurrence time is clear (*Table 5*, *Fig. 4*).

According to prospective controlled trials[19,20], there is no established efficacy of arterial chemoembolization in prolonging the life of patients with HCC. In contrast, although it has never been assessed for recurrent HCC, percutaneous alcohol injection could be proposed for a

Table 7 Review of reports on repeat hepatectomy for recurrent hepatocellular carcinoma

Reference	Year	Total no. of of resections	No. of recurrences	No. of repeat hepatectomies	Operative death	5-year survival after first operation (%)
Zhou *et al.*[11]	1993	392	185	65 (35)	0	42
Kakazu *et al.*[12]	1993	258	209	24 (11)	0	87
Matsuda *et al.*[13]	1993	100	36	22 (61)	0	51
Suenaga *et al.*[15]	1994	134	74	18 (24)	0	45
Present series	1995	290	167	50 (30)	5 (10)	41

Values in parentheses are percentages

single nodule of less than 5 cm[21,22]. Based on these criteria, 35 of 50 patients of the present series would have been eligible for percutaneous alcohol injection. A prospective randomized study is undoubtedly needed to clarify this subject.

The authors previously reported 229 radical hepatic resections for HCC[23]. Among the patients who had lesions smaller than 5 cm and were aged less than 60 years, there were 26 patients with liver cirrhosis of Child grade B and C, and another six patients had two or more HCC nodules in different lobes or segments irrespective of the Child grade. These 32 patients were considered retrospectively as appropriate candidates for liver transplantation. Their 5-year survival rate after hepatic resection was only 16 per cent. This was much worse than that of transplantation in similar patients[6,7].

The present study has shown that repeat hepatectomy has a limited role in the treatment of recurrent HCC. Small recurrent tumours in the liver can be detected by careful follow-up of patients after the first hepatectomy. Many such patients without extrahepatic spread could potentially be saved more effectively by liver transplantation. Considering the shortage of livers for transplantation, repeat hepatectomy should probably be continued, but only for selected patients with a solitary tumour and Child grade A liver disease.

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Erratum

J. F. Stebbing, D. P. Jewell, M. G. W. Kettlewell and N. J. McC. Mortensen. Long-term results of recurrence and reoperation after strictureplasty for obstructive Crohn's disease. *British Journal of Surgery* 1995; 82: 1471–1474.

The title should read: Recurrence and reoperation after strictureplasty for obstructive Crohn's disease: long-term results.

British Journal of Surgery 1996, 83, 132–138

Correspondence

Budd–Chiari syndrome

Sir

We read the Review by Dr Tilanus (*Br J Surg* 1995; 82: 1023–30) with much interest, and would like to comment further on some aspects of the surgical management of Budd–Chiari syndrome by portasystemic shunt. The technical demands of the side-to-side portacaval anastomosis are emphasized in the article, especially in patients with caudate lobe hypertrophy. Although several alternative strategies to overcome these problems were proposed, no mention was made of the technique first described by Erlik and colleagues in 1963[1], in which an end-to-side anastomosis between the left renal and portal veins was carried out in five patients. This technique involves division and oversewing of the left renal vein on the caval side of the left adrenal vein origin to preserve venous return from the left kidney via adrenal, gonadal and other retroperitoneal collaterals. The cut end of the proximal left renal vein is anastomosed to the side of the portal vein and acts as a large-calibre, autologous inflow conduit to the inferior vena cava through a single, tension-free anastomosis. This manoeuvre overcomes the limitations of access associated with caudate lobe enlargement, a short extrahepatic portal vein or anatomical distortion, and avoids any resort to the various portacaval interposition grafts or mesocaval shunts. Lewis and colleagues[2] highlighted the lack of wider recognition of this technique in their report of the portarenal shunt in six patients with intractable ascites, variceal haemorrhage and/or hepatic dysfunction complicating hepatic cirrhosis or Budd–Chiari syndrome.

We have performed end-to-side portacaval shunting via the interposed left renal vein in two patients. The first patient was a 29-year-old woman who presented with acute Budd–Chiari syndrome secondary to antiphospholipid antibody syndrome 7 weeks after childbirth. At operation, side-to-side portacaval anastomosis was precluded despite partial resection of an enlarged caudate lobe, and a side-to-end portarenal shunt was performed. The patient made an uncomplicated recovery and remains asymptomatic with Doppler ultrasonographic evidence of shunt patency and normal kidneys 2 years later.

The second patient was a 43-year-old man with a 15-year history compatible with alcohol-related cirrhosis and Budd–Chiari syndrome who presented with recurrent episodes of variceal haemorrhage and refractory ascites. Hepatic vein thrombosis and inferior vena caval patency were confirmed by Doppler ultrasonography and cavography. An attempt at transjugular intrahepatic portasystemic stent shunt (TIPSS) insertion failed because of an inability to negotiate the hepatic vein occlusions. At operation, side-to-end portarenal shunt construction was necessitated by caudate lobe enlargement There were no postoperative complications, and the patient remains well with complete resolution of ascites, no further variceal bleeding and normal renal function 8 months later.

In each patient intraoperative manometric measurement of portal vein and inferior vena caval pressures was used to demonstrate satisfactory portasystemic pressure gradients before and after shunt creation. In addition, we found intraoperative ultrasonography a useful method for confirming retrohepatic caval patency without resort to intraoperative cavography.

We recommend this ingenious but neglected modification of the conventional side-to-side portacaval shunt. It is a useful technique which seems particularly suited to the treatment of patients with hepatic cirrhosis and intractable ascites, or the Budd–Chiari syndrome with thrombosis confined to hepatic veins, where a 'central' portasystemic shunt is desired but anatomical circumstances preclude conventional side-to-side portacaval shunting.

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1 Erlik D, Barzilai A, Shramek K. Portarenal shunt. A new technique for portasystemic anastomoses in portal hypertension. *Ann Surg* 1963; 159: 72–8.
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Author's reply

Sir

I thank Mr John and colleagues for their comment and interest in this article. The portarenal shunt has been described in five patients with Budd–Chiari syndrome over the past 30 years, so it is rarely used. There is no doubt that direct side-to-side portacaval shunt is the procedure of choice in uncomplicated Budd–Chiari syndrome, even in patients with hypertrophy of the caudate lobe. Only in rare cases is a portacaval or mesocaval shunt performed, homologous jugular vein being better than protheses. The procedure described by John *et al.* is a possible alternative for patients in whom a mesoatrial shunt is indicated in Budd–Chiari syndrome with occlusion of the inferior vena cava.

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Efficacy of tumoricidal agents *in vitro* and *in vivo*

Sir

It was with great interest that I read the article by Mr Docherty and colleagues (*Br J Surg* 1995; 82: 1050–2).

We undertook a similar study 5 years ago[1] using DHD/K12 colon cancer cells and male syngeneic BD IX rats. When 10^6 of these cells were injected intraluminally as an enema they implanted in 30 per cent of the animals at the serosal site of a colonic anastomosis (constructed after instillation of the tumour cells) and developed into a tumour without invading the colonic mucosa. When both bowel segments were swabbed with different tumoricidal agents before the anastomosis, only the administration of sodium hypochlorite 0·2 per cent significantly reduced the tumour cell implantation rate (8 per cent; $P < 0·01$, χ^2 contingency test).

We recommend the use of sodium hypochlorite 0·2 per cent for patients undergoing colorectal cancer surgery. We use it for bowel lavage before anastomosis and at the end of the operation when the peritoneal cavity is washed with this solution.

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Port site metastases after laparoscopic colorectal surgery for cure of malignancy

Sir

We read with interest the correspondence concerning the Review by Drs Wexner and Cohen (*Br J Surg* 1995; 82: 295–8) and share a belief in the hypothesis suggested by Dr G. Kazemier and colleagues which they have named the 'chimney effect' (*Br J Surg* 1995; 82: 1141–2). We wonder whether they have any evidence that the carbon dioxide contains an aerosol of tumour cells.

Airborne particulate matter has been proposed as a possible mechanism for trocar site metastases in a recent review[1]. We have been collecting the smoke produced by electrocoagulation during laparoscopic surgery. To the naked eye the smoke contains visible particles which fill the pneumoperitoneum and cloud the operative field. Previous workers have found viral particles[2,3] and numerous carcinogens[4] in surgical smoke during non-laparoscopic surgery. We believe that we are the first to find clumps of whole cells in smoke. The pneumoperitoneum concentrates the smoke and keeps it humid, which may preserve the cells.

During a number of laparoscopic procedures we have aspirated the smoke through a moist filter. The tubing and filter are then washed with a buffered solution. Centrifugation of the liquid sample yields clumps of whole cells, which we have been able to identify using immunohistochemical stains. Work continues with direct electron microscopy of the filters and biopsies of trocar sites to confirm the implantation of the cells carried by the carbon dioxide that leaks around the trocars.

There are ethical considerations that limit the intentional coagulation of malignant tissue in the clinical setting, but *in vitro* models and animal studies may shed more light on whether malignant cells can be carried in aerosol form, and on their role in trocar site metastases.

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Introduction of laparoscopic cholecystectomy in a large teaching hospital: independent audit of the first 3 years

Sir

We were interested to read this paper (*Br J Surg* 1995; 82: 968–71) but take issue with the authors' two main conclusions. First, they state that their figures for conversion rate (19 per cent overall) and bile duct injury (1·2 per cent) are likely to be representative of the situation in the surgical community at large In our practice area of 300 000 population, three of four general surgeons have performed 525 laparoscopic cholecystectomies in the past 3 years using an 'all comers' policy. The overall conversion rate was 3·05 per cent (range 1·98–9·75 per cent) with one bile duct injury (0·19 per cent).

Their second conclusion appears to be that specialization in laparoscopic cholecystectomy is not achievable in practice and that consequently the results for specialist centres such as Leeds cannot be matched in the general surgical community. We would respectfully suggest that with 12 general surgeons in Nottingham it should be entirely possible for a small number to specialize in laparoscopic surgery. In our series 80 per cent of operations were performed by one surgeon.

Laparoscopic cholecystectomy was initially more difficult than the open procedure. However, our experience has shown that the learning curve is relatively short and once this hurdle is cleared, conversion and bile duct injury should be relatively rare events Indeed, we suggest that conversion and bile duct injury rates together represent a good yardstick of surgical competence in this technique.

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Authors' reply

Sir

Many thanks for giving us the opportunity to reply to this letter. We would like to congratulate the surgeons at Broomfield Hospital on their excellent results but, with the greatest respect, we suggest that they convey a similar message to ours Their conversion rates varied between 2 and 10 per cent by individual surgeon and, as 80 per cent of the operations were performed by one of them, this implies that two surgeons were 'dabbling'

We do not try to excuse our results – our intention was to describe how laparoscopic cholecystectomy evolved in our hospital so that others might avoid the pitfalls that we encountered. As a result of our experience, we strongly endorse the Broomfield surgeons' view on specialization and, indeed, we have now implemented this at our hospital.

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Mobility after lower-limb amputation

Sir
I read with interest the article by Mr Collin and Ms Collin (*Br J Surg* 1995; 82: 1010–1) but comment is required as it is rather misleading. Manchester subregional prosthetic centre data indicate that 85 per cent of amputees have either peripheral vascular disease or diabetes; the overall prevalence of diabetes is 35 per cent in this population. After holistic rehabilitation assessment and prosthetic management, even elderly amputees will be able to decrease the level of dependency because of the ability to transfer, stand and achieve some indoor mobility. Decrease in dependency is a notable objective to decrease the level of handicap. Even though patients who achieve walking ability after amputation may become wheelchair-dependent within 5 years, it is important that they have a good quality of life during this time and beyond, albeit from a wheelchair. It would be tragic and inappropriate if the wrong message was given, namely that it is best to forego prosthetic rehabilitation and issue elderly amputees with wheelchairs

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Authors' reply

Sir
We agree with the comments of Mr Kulkarni which accord with those expressed in our article. Prosthetic limbs should be supplied to most amputees, and walking training should be offered to all who might benefit. The important message to remember is that almost all elderly vascular amputees supplied with a prosthetic limb will also need to use a wheelchair at least some of the time. The commonest mistake in the rehabilitation of amputees is to assume that patients who can walk in a gymnasium with a prosthetic limb do not need to have their environment adapted and receive training for wheelchair use.

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J. Collin

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Splenic abscess

Sir
We read with interest the Short Note by Dr Herman and colleagues (*Br J Surg* 1995; 82: 355) concerning the diagnosis and treatment of splenic abscess.

While we would agree that modern imaging techniques such as ultrasonography and computed tomography have led to earlier diagnosis of this unusual infective problem, we do not agree that percutaneous drainage or aspiration and splenectomy are the only methods of treatment.

We cite the case of a patient with polyarteritis nodosa and splenic abscess who was receiving immunosuppressive agents and in whom percutaneous drainage failed to control the sepsis. At laparotomy the spleen was enlarged and embedded in dense adhesions This condition was treated by splenotomy evacuation of the abscess and omental packing of the resultant cavity. The patient made an uneventful recovery and remains well 3 years later.

It is disappointing that the authors did not mention this modality of treatment which is more effective than percutaneous drainage and aspiration, and may avoid a potentially dangerous and difficult splenectomy in an unfit and immunosuppressed patient.

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Author's reply

Sir
I am pleased that our Short Note has been of interest, and I am glad to be able to discuss the suggestions of Messrs Carr and Nehra.

Splenotomy and abscess evacuation can undoubtedly be considered a therapeutic option for the disease, but it is an unusual procedure. Based on our own experience, we agree with other authors[1,2] that splenectomy is the best treatment for splenic abscess. Percutaneous drainage may be performed in selected patients (e.g. unilocular abscess) or as a primary approach in patients who are at high surgical risk. Splenotomy can be considered in case of failure of the percutaneous approach and (as in the case described) if splenectomy is technically difficult because of severe adhesions, but the risk of bleeding with this procedure should not be neglected.

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1 Gadacz TR. Splenic abscess. *World J Surg* 1985; 9: 410–15.
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Technique for closure of port sites under laparoscopic visual control

Sir
We read with interest the recent Surgical Workshop by Messrs Cole, Vipond and Espiner (*Br J Surg* 1995; 82: 1134–5) illustrating their technique for closure of port sites under laparoscopic visual control.

We note that this technique involves tying two knots in the suture to close the defect. We use a similar technique in which only one length of polydioxanone suture is used. The awl is used to pass the suture into the abdomen as shown in their illustrations, but the suture is left free in the abdomen instead of being exteriorized via the cannula. The unloaded awl is then passed through the abdominal wall on the opposite side of the defect, and the suture is threaded through the awl within the abdomen using the petelin forceps. The awl is withdrawn through the abdominal wall and the suture can be tied externally, leaving only one knot in the loop.

We have found this to be an easy procedure and suggest it is a simpler way of achieving a stronger closure than that described in the article.

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Authors' reply

Sir
Thank you for giving us the opportunity to read the letter by Messrs Chaloner and Heath in response to our recent Surgical Workshop concerning the technique of closure of port sites at laparoscopic surgery. We were delighted to hear that they have found this method of closure as simple as we have, and we were most interested in their variation using polydioxanone suture material. As we used polyglactin, internal threading was not an option, but as we have now tried polydioxanone and found it as straightforward as they indicate, we may consider incorporating it as 'advanced skills training' for our senior house officers!

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Exfoliative cytology in the diagnosis of breast disease

Sir
Nipple discharge is a common problem in our breast unit. We require the discharge to be unilateral, uniductal and spontaneous before performing cytology and ductography. Only rarely do we encounter a case of bilateral uniductal or multiductal discharge that is truly spontaneous. It is then essential to take slide material from each orifice separately to ensure there is no crossover of material from adjacent ducts.

Mr Dunn and colleagues (*Br J Surg* 1995; 82: 789–91) must surely be using the term 'expressible' nipple discharge synonymously with 'spontaneous' or 'easily expressible' discharge (expressed with minimal pressure to the nipple or relevant segment).

Many women in our clinic present with multiductal (often bilateral) serous or colostrum discharge. We are often amazed at the pressure that they employ. As long as clinical, mammographic and ultrasonographic studies (where appropriate) are clear, we reassure them and follow up without performing cytology.

A problem of particular interest to us has been the patient with discharge elicited by herself with extreme pressure, which appears grossly bloody in nature. Cytology often shows inflammatory cells together with erythrocytes. More than one duct may show similar findings. Once again, in the absence of a dilated duct at ultrasonography and with normal clinical and mammographic features, these patients are followed routinely without further intervention. Once they stop checking themselves the erythrocyte content, in our experience, usually disappears.

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Author's reply

Sir
In reply to Dr Strano, I am keen to amplify our approach to nipple smears. Certainly a few patients reported spontaneous discharge, but this symptom tends to be intermittent and often digital expression was necessary to obtain a sample in the clinic. The massage was always gentle and brief – as stated – and only to the areola and papillary regions.

We are aware that the appearance of multiple duct discharge can differ. Initially a 'total smear' is made, followed by a specifically directed sample from any duct where fresh or altered blood or serous discharge is evident. This is easily done by scraping the duct orifice with the corner of a microscope slide.

We have been spared the spectre of women inducing 'artefactual' bloody discharge by 'extreme pressure', and in the event would feel it our duty to discourage such behaviour. Two patients were seen with unilateral gross spontaneous bleeding which appeared to derive from fibroadenomas harbouring epithelial atypia, a feature invariably confirmed by histopathological examination.

Our experience would not lead us to be restrictive in seeking nipple discharge and cytology. Taken overall, the microscope was more precise than the naked eye, and gentle exfoliative cytology should be encouraged.

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Influence of screening on the incidence of ruptured abdominal aortic aneurysm: 5-year results of a randomized controlled study

Sir
Mr Scott and colleagues (*Br J Surg* 1995; 82: 1066–70) have shown a 42 per cent reduction in mortality rate from abdominal aortic aneurysm (AAA) in men invited for screening compared with controls. It is noteworthy that ruptured AAA accounted for 3·1 per cent of all deaths in their control group, a proportion more than twice that recorded nationally using the same data base[1]. If deaths from ruptured AAA in the Chichester sample had been more representative of those in the age-matched control population of England and Wales, the data would have suggested that screening for AAA increases the risk of death from the disease. The authors are wise to conclude that a large multicentre trial is required to test the value of screening for AAA.

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1 Office of Population Censuses and Surveys. *1991 Mortality Statistics Cause*: 2–97.

Clinical outcome and restenosis following percutaneous transluminal angioplasty for ischaemic rest pain or ulceration

Percutaneous transluminal angioplasty for lower-limb critical ischaemia

Sir
We read with interest the articles by Mr Ray and colleagues (*Br J Surg* 1995; 82: 1217–21) and Mr London and colleagues (*Br J Surg* 1995; 82: 1232–5). Our experience of percutaneous transluminal angioplasty (PTA) in patients with critical limb ischaemia in a district general hospital has been broadly similar. A prospective evaluation of 43 patients with critical limb ischaemia, Fontaine III/IV, who underwent PTA between January 1991 and December 1994 was undertaken. Eleven patients had rest pain, 14 had ulceration and 18 had digital gangrene. During the study seven patients died from 'unrelated' disease. Primary patency as judged clinically and by duplex scanning was 74, 48 and 5 per cent at 6, 12 and 36 months

respectively. Ten per cent of the group required augmentation surgery and 10 per cent had major amputation at 4, 5, 14 and 18 months after PTA. We agree that PTA in suitably selected patients with critical limb ischaemia can be successful in avoiding major amputation. Our experience of restenosis after PTA is that it may not be an important clinical problem presumably because angioplasty has allowed time for a collateral arterial circulation to develop.

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Risk-adjusted analysis of surgeon performance: a 1-year study

Sir

I would like to point out that there is some confusion over the idea of confidence limits in this article by Mr Copeland and colleagues (*Br J Surg* 1995; 82: 408–11). Confidence limits or intervals are limits or intervals for population parameters based on sample statistics. For example, in *Table 3* for surgeon A the ratio of observed (O) to expected (E) deaths is 32 : 31 = 1·03. A 95 per cent confidence interval (c.i.) for the underlying ratio can be calculated using the tables in the article by Gardner and Altman[1]. Assuming O follows a poisson distribution, the lower and upper limits for a 95 per cent c.i. for the unknown mean are 21·888 and 45·174 which yield a 95 per cent c.i. for O/E of 21·888 : 31 = 0·71 and 45·174 : 31 = 1·45 (O is written as x in the tables referred to). This approach is approximate, but given a large number of operations and a small number of deaths, it is likely to be reasonably accurate. Clearly in the above case the ratio 1 lies within the 95 per cent c.i. and thus there is no evidence that surgeon A's death rate differs from what is expected using the POSSUM (Physiological and Operative Severity Score for enUmeration of Mortality and morbidity) assessment.

In addition, it should be pointed out that in *Table 9* it is incorrect to label as NA (not applicable) those ratios in which the observed number of complications is 0. These ratios should be given as 0 for surgeon A (urological) and surgeon C (breast and endocrine). NA should be reserved for those situations in which results are genuinely not available, i.e. for non-urological operations for the urological specialist surgeon E.

From the data given in the paper it is not possible to be certain that the O/E rate for miscellaneous procedures for surgeon C is truly significantly different from 1. However, even if this is a significant difference, there is a total of 25 comparisons for different surgeons and procedures possible (excluding those results genuinely not available from surgeon E) and to find one result significant at a significance level of 0·05 would not be too surprising.

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1 Gardner MJ, Altman DG. Statistics with confidence. *BMJ* 1989; 208: 116–17.

Author's reply

Sir

I agree with Mr Gibbs' comments with regard to assessing confidence limits. I also agree that surgeon A is performing well within his confidence limits and therefore his death rate does not differ from that expected, as was quite clearly illustrated in the paper.

I would accept his comments with regard to the non-application. It is important that all people involved in producing quality standards realize that predictive assessments of mortality and morbidity rates carry confidence limits, otherwise quality decisions may be taken which are in error, and I think Mr Gibbs is reinforcing this fact.

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The Wilcoxon–Mann–Whitney test condemned

Sir

I recently had occasion to review the methods of statistical analysis used in consecutive original articles published in five biomedical journals during the first half of 1993. These were *The British Journal of Surgery*, *Annals of Surgery*, *American Journal of Physiology*, *Circulation Research* and *British Journal of Pharmacology*. In *The British Journal of Surgery* the non-parametric Wilcoxon–Mann–Whitney test was used approximately twice as often as the Student's *t* test for comparing the central tendencies of two independent groups, whereas the reverse was the case in all other journals. I could find no explanation for this discrepancy. The sorts of experiments described in *The British Journal of Surgery* were not notably different from those in the other journals, their authors gave no explanation for preferring one test to the other, and *The British Journal of Surgery*'s statistical guidelines give no encouragement to do so[1].

The Wilcoxon and Mann–Whitney tests are exactly equivalent. In both, continuous data are transformed into rank order. It is widely supposed that this makes the Wilcoxon–Mann–Whitney test superior to Student's *t* test if the samples come from non-normally distributed populations. But this and other advantages sometimes claimed for the test are illusory.

The most serious difficulty with the Wilcoxon–Mann–Whitney test requires a fairly technical explanation. The outcome of statistical testing is usually expressed as a *P* value or the equivalent confidence interval. The *P* value indicates the risk of Type I error: in other words, it is the probability that the null hypothesis is falsely rejected. One could describe this as the risk of making a false-positive statistical inference. Most biomedical researchers believe that every effort should be made to avoid false-positive inferences. That is, the tests we use should be 'robust' against a probability of Type I error which exceeds that nominated as the level of significance, conventionally $P = 0·05$.

The conditions under which Student's *t* and the Wilcoxon–Mann–Whitney tests are, or are not, inaccurate are practically identical. The tests are in fact equally robust against excessive Type I error when the sampled populations are non-normally but symmetrically distributed, although only when certain conditions are fulfilled[2]. Neither test is robust when the population variances are unequal, especially if the sample sizes are also unequal[2]. Specifically, if the smaller sample comes from the population with the greater variance, the risk of Type I error is inflated[2–4]. In the articles reviewed in *The British Journal of Surgery*, the sample variances were as often grossly unequal as they were approximately equal. In the former case the statistical inferences are likely to have been flawed.

In short, the Wilcoxon–Mann–Whitney test gives no more protection against false-positive statistical inferences than does Student's t test. It has two other weaknesses: (1) it is designed to detect a difference between two mean-ranks. Under the ranking system employed, mean-ranks correspond neither to means nor medians, so the statistical inference is vague; (2) in most microcomputer statistics packages the test statistic is evaluated by a normal approximation, an inaccurate method when experimental groups are small.

What alternatives are there to these tests if the spread of data within the two groups is markedly unequal or skewed, or if the groups are small or unequal in size? Welch's modification of Student's t test is very effective in coping with inequality of population variances[2], is described in most statistical texts and is available in many microcomputer statistics packages. An analogous modification to the Wilcoxon–Mann–Whitney test has been suggested, but it is less robust against excessive Type I error than the Welch test, and it is not easy to perform[2].

The Wilcoxon–Mann–Whitney and t tests are inaccurate if the assumptions on which they depend are breached and because the inferential model on which they are based assumes random sampling of defined populations. Random sampling is rarely employed in biomedical research. Instead, the experimental units (patients, animals, tissues or cells) are randomly divided into groups that are then exposed to different treatments or conditions. In this circumstance the proper inferential model is the randomization one, and the valid tests of significance are exact randomization or permutation tests for differences between means or other indices of central tendency[5].

I urge surgical researchers to abandon the Wilcoxon–Mann–Whitney test, unless they have measured up their results on a rank-order scale. Instead, I suggest they use one of the options mentioned above: a randomization (permutation) test if they are dealing with randomized groups or the Welch modification of Student's t test if they employ random sampling.

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1 Murray GD. Statistical guidelines for The British Journal of Surgery. *Br J Surg* 1991; 78: 782–4.
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Reply from *BJS* Statistical Adviser

Mr Ludbrook's letter is based on an observation with which I wholeheartedly agree, namely that the validity of any statistical analysis is crucially dependent on the validity of the assumptions underlying that analysis. However, I do not agree that this implies that our authors should abandon the (Wilcoxon-)Mann–Whitney test.

The selection of an appropriate statistical test requires experience and insight, and one must be wary of a proscriptive cookbook approach. When comparing two samples, one needs to compare both distributional shape (in particular, are the data skewed?) and variability. If the distributions are symmetrical, then there is no great problem, and the Welch modification of the Student's t test is likely to be a sound choice. However, this statement begs the question of how symmetrical is symmetrical, and how large a sample size is required before one can be secure in assuming symmetry? This matter interacts with prior expectations. For example, if analysing data from a therapeutic trial in patients with mild essential hypertension, I would generally be happy to assume that the reductions in blood pressure would be symmetrical without even looking at the data, whereas if I were analysing creatinine levels in patients with mild renal failure, I would be very unhappy with assuming symmetry, even if a histogram based on a small sample of patients showed no gross evidence of skewness.

Mr Ludbrook says very little about how to analyse skewed data, this being precisely the situation where the Student's t test (with or without the Welch modification) breaks down, and where the Mann–Whitney test is potentially more reliable At the very least, if an author is using the Mann–Whitney test to analyse skewed data it means that it is likely the data will be presented using informative summary statistics (median and interquartile range) rather than the all too common but misleading mean and standard deviation.

Another approach to analysing skewed data is to consider a transformation of the data. Surprisingly often it is possible to find a transformation that will simultaneously give data which are symmetrical and have similar variability in the two groups, allowing a sensitive comparison based on a conventional Student's t test. However, unless the transformation happens to be a logarithmic one, there are problems in interpreting the resulting confidence interval.

The question of variability is also an important one However, with small sample sizes it can be difficult to distinguish between differences in variability and skewness The data could come from identically shaped, skewed distributions, but if one sample contains say two observations which are well into the tail of the distribution whereas the other sample contains no such observations, this could suggest (wrongly) that there is a substantial difference in variability between the two samples. This point again highlights the need for insight into the underlying data.

If, on the other hand, one has large samples which are symmetrical and in which the variability is clearly different, one has to ask whether the Welch modified Student's t test is actually answering a sensible question. If there is a gross imbalance in variability is this not of interest in itself? It is simple to envisage clinical situations where the effect of an intervention would be to reduce the variability of an outcome measure. In such situations, it might be more sensible to perform a test that compares the variability, rather than burying this difference, as would be done with a Welch modified Student's t test Yet again, what is needed is insight into the clinical situation, not statistical dogma.

In summary, the choice of an appropriate statistical procedure requires both an understanding of the strengths and limitations of the different procedures, and also a deep understanding of the clinical context. I wonder whether Mr Ludbrook has considered an alternative explanation for the high level of usage of the Mann–Whitney test by authors in *The British Journal of Surgery*? The data are at least consistent with the hypothesis that under the guidance of a statistically astute Editorial Board, our authors have already taken on board the message that one should think critically about one's data rather than reaching woodenly for the nearest t test.

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New concepts in the pathophysiology of oxygen metabolism during sepsis

Sir

We read with interest the excellent Review by Messrs Vlessis, Goldman and Trunkey (*Br J Surg* 1995; 82: 870–6) The authors propose intriguing new concepts in the pathophysiology of oxygen metabolism during sepsis. In particular we welcome their exhortation for increased interest to be shown in the role of reactive oxygen generation and metabolism during sepsis. There are however several points about which we would like to comment.

In so far as the fate of phagocyte-derived reactive oxygen species are concerned, the article makes no mention of the neutrophil (PMN) degranulation enzyme myeloperoxidase (MPO). MPO gives the PMN its green colour and constitutes 5 per cent of its dry weight[1]. On stimulation, PMN not only undergoes activation of its membrane-bound nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system but also degranulates. One of the major events of PMN degranulation is the extracellular release of MPO. The peroxide (H_20_2) produced by NADPH oxidase activation can now react with halide and hydrogen ions under the influence of MPO to produce hypohalides, particularly hypochlorous acid (HOC1). This system is of considerable importance, HOC1 being a powerful oxidant that can attack a wide variety of molecules that are both innate and foreign to the host. HOC1 is also considered to be the most potent PMN antibacterial and antifungal agent.

It is surprising that the authors concentrate their discussion on the activities of products such as H_20_2 and the hydroxyl radical (OH^-). As there is clearly a further potent metabolic pathway for the reduction of H_20_2, it seems unlikely that the capacity for detoxification of H_20_2 would be overwhelmed before end-stage sepsis. The scant evidence for *in vivo* production of OH^- counterbalanced by animal and human studies demonstrating upregulation of PMN ability to produce H_20_2 and HOC1 following septic stimulation (such as by bacteria, lipopolysaccharide and tumour necrosis factor) calls into question any important role for OH^- in septic states.

The authors call for a new understanding and the use of alternative fuels in sepsis treatment. Recognition should be given, not only to glutamate and its role in detoxifying H_20_2, but similarly to taurine, the most abundant amino acid available *in-vivo*. Taurine is an avid scavenger of HOC1. Recent work suggests that patients who suffer from the capillary leak syndrome consequent upon interleukin 2 therapy derive benefit from exogenous taurine[2].

Finally the effects on non-steroidal anti-inflammatory drugs (NSAIDs) on the phagocyte response in the sepsis syndrome have previously been described[3]. These drugs have the dual effect of diminishing the migration of activated PMN across damaged endothelial cell barriers in animal models of sepsis-induced microvascular injury as well as curbing the production of phagocyte long-lived oxidant production. NSAIDs are cheap and widely available, and their role as biological response modifiers in sepsis should be studied in more detail in controlled clinical trials.

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1 Weiss SJ. Tissue destruction by neutrophils. *N Engl J Med* 1989; 320: 365–75.
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Authors' reply

Sir

I am grateful for the interest in our recent Review. Unfortunately, an all-encompassing review of oxygen metabolism in the sepsis syndrome would exceed the space restraints of the Journal by an order of magnitude. As such, several interesting topics worthy of discussion (e.g. nitric oxide, cytokines, prostaglandins etc) were not included. With this in mind, I have a few brief comments regarding the above statements of Messrs Delicata, Roy and Cary.

First, myeloperoxidase may well play a role in tissue destruction and organ dysfunction, and during sepsis. Two important distinctions, however, between nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and myeloperoxidase must be appreciated in this regard. The NADPH oxidase activity is initiated on antigen contact and stops after phagocytosis is complete. Therefore, a large quantity of H_2O_2 is released extracellularly. In contrast, degranulation and hypochlorous acid production is primarily contained within the phagosome itself[1]. Second, I do not propose a primary role for OH^- in sepsis. I emphasize that significant cellular dysfunction occurs following the reduction of H_2O_2 alone and that OH^- is formed from O_2^- and H_2O_2. Third, I share your enthusiasm for the antioxidant activities of taurine, however, these aspects remain unstudied with respect to sepsis. Finally, I am aware of a good multicentre clinical trial of NSAID therapy in sepsis which showed no therapeutic benefit[2].

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British Journal of Surgery 1996, 83, 139–141

Book reviews

Vascular Imaging for Surgeons

R. M. Greenhalgh (ed). 250 × 172 mm. Pp. 531. Illustrated. 1995. London: W. B. Saunders. £90.

This is the latest in a series of books compiled by Roger Greenhalgh in conjunction with the annual Charing Cross Vascular Symposium. The format follows its predecessors, with invited symposium speakers providing a corresponding book chapter. Publication to coincide with the symposium ensures that its contents are current in a rapidly changing field. Sections deal with carotid arteries, the aorta and its branches, peripheral vessels and the venous system, with a useful general introduction. Inevitably, there is some repetition as variations of contrast imaging, computed tomography and magnetic resonance imaging feature frequently. However, the book fulfils well its stated aim of indicating strengths and weaknesses of available imaging methods in any given application and each chapter is complete in itself. The authorship is international and chapters range in content from reviews of currently available imaging methods to descriptions of the experimental and exotic. Where necessary, there are sufficient mathematical formulas to explain basic principles but we are spared complex physics. As a source of reference material for further reading, this book will prove invaluable. With few exceptions, the quality of illustrations, both coloured and monochrome, is high and I was impressed by the liberal use of simple juxtaposed line drawings to explain some of the more complicated original images. The book provides a critical, thorough and up-to-date review of what is available in vascular imaging and an insight into what may be possible in the future. It is aimed at the practising vascular surgeon who will find it readable, interesting and informative.

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Clinical Problems in Gastroenterology

J. M. Rhodes and H. H. Tsai (eds). 261 × 193 mm. Pp. 307. Illustrated. 1995. London: Mosby-Wolfe. £29·95.

The authors have structured this book to relate to problems frequently encountered by gastroenterologists; they consider clinical problems, devote chapters to signs, and then tackle various aspects like abnormal liver biochemistry and paediatric conditions. Although at first sight the chapter headings appear rather random, they nevertheless address the difficulties that clinicians face. Each chapter starts with a helpful approach – 'reaching a diagnosis' – and proceeds to discuss some of the conditions in greater detail. This is sound but, because of the avoidance of repetition of detail, the reader may need to refer to another chapter (sometimes several); this is compensated by the presence of a good index. I personally do not regard this feature as a disadvantage and feel that this new diagnostic approach is valuable. The summary tables are particularly helpful. The radiographs on the whole are good, although those in the section on jaundice have lost clarity in reproduction and would be helped by line diagrams for explanation. My main criticism is that, for the gastroenterologist surgeon, there is little emphasis on surgery and some aspects are debatable. The latter is true of the application of barrons bands and the Thiersch operation, and the chapter on nausea and vomiting scarcely mentioned gastric outlet obstruction. These are the sort of points that need attention in the second edition. This is an enjoyable book with a new approach. It will be helpful for the surgeon at the beginning of training who aims to specialize in gastroenterology, but it does not provide the depth of detail required for the Inter-Collegiate Specialty Examination of the Royal Colleges of Surgeons.

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Principles of Laparoscopic Surgery. Basic and Advanced Techniques

M. E. Arregui, R. J. Fitzgibbons Jr, N. Katkhouda, J. B. McKernan and H. Reich (eds). 285 × 220 mm. Pp. 852. Illustrated. 1995. Heidelberg: Springer. DM298.

This is really the first textbook of laparoscopic surgery. The editors have asked a select group of expert surgeons to present what amounts to an encyclopaedic account of current laparoscopic surgical practice. Not only are varying surgical viewpoints presented, but gastroenterologists and radiologists also describe alternative methods of management. The authors have divided the book into four sections. Section I provides essential information on equipment and basic techniques; nursing and anaesthetic considerations are discussed in detail. In Section II various organ systems are considered, with minimally invasive techniques that include not only different laparoscopic approaches, but also endoscopic and radiological options. Section III describes the important developments in the specialty areas, with an extensive examination of gynaecology and urology. Angioscopy in venous and arterial intraluminal surgery provides a window to potential developments that may find applications in abdominal surgery. Section IV deals extensively with technology (electrocautery, fibreoptic, video-camera) presently being used and provides an insight into potentially useful future technology (laser, shockwave). Potential complications are described with help for surgeons to avoid the pitfalls that lead to these. This book is a reference book; it is a detailed, authoritative work that should be of great use to both novice and advanced laparoscopic surgeon.

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Fundamentals of Laparoscopic Surgery

L. W. Way, S. Bhoyrul and T. Mori (eds). 235 × 160 mm. Pp. 271. Illustrated. 1995. New York: Churchill Livingstone. £30.

This book has been written to provide a thorough basis for those wishing to employ laparoscopic techniques. The authors have managed to compose a book which guides the reader through the basic laparoscopic procedures in a practical and instructive manner. The complex technical design and limitations of video-endoscopic equipment, insufflator and laparoscopic instruments are presented in a comprehensive and readable way. The technique of establishing a pneumoperitoneum, insertion and placement of trocars, use of various laparoscopic instruments and laparoscopic suturing are described in a clear and detailed fashion. Numerous illustrations aid the reader in understanding these techniques. The authors share their great experience in laparoscopic surgery with the reader in the sections on trouble-shooting and prevention of complications; these sections are invaluable and should enable the reader to avoid or solve minor and major problems arising during laparoscopic surgery. This volume provides an up-to-date source on available laparoscopic techniques and sheds some light on future developments. *Fundamentals of Laparoscopic Surgery* is an excellent book which should appeal to both beginners and those already practising laparoscopic surgery. It excels in its practical approach.

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Urinary Diversion, Scientific and Clinical Practice

G. D. Webster and B. Goldwasser (eds). 282 × 222 mm. Pp. 351. Illustrated. 1995. Oxford: Isis Medical Media. £69·95.

This is an outstandingly good book which all urologists interested in techniques of urinary diversion should buy. It is difficult to appreciate how recently it was that these operations became widely available. It was not until the 1930s that Grey-Turner regularly and safely carried out ureterosigmoidostomies in England. The ileal conduit described by Eugene Bricker in the 1950s was such a successful operation even when practised by surgeons of widely differing skills that few thought about other types of urinary diversion; this has changed in the past 15 years. Various factors have led to an intense interest in bladder reconstruction, including the advent of clean intermittent self-catheterization to empty urinary reservoirs, the creation of low pressure urinary reservoirs from detubularized segments of bowel, the availability of artificial urinary sphincters to provide a continent urethra, and the development of different techniques, such as those described by Kock and Mitrofanoff, to produce mechanisms allowing continence when reservoirs are connected to skin. Bladder reconstruction rather than ileal conduit formation can now be offered to most patients with neuropathic bladder disease and those undergoing cystectomy for bladder cancer. George Webster and Benad Goldwasser have attracted many leading reconstructive urologists to produce a comprehensive and beautifully presented book on urinary diversion.

Topics cover the whole range of urinary diversion including its history, side-effects, indications, types (ileal conduit, bladder replacement and continent reservoirs), the question of whether refluxing ureteric anastomoses is safe, and the possible development of the artificial bladder. Criticisms are minor and one feels a little churlish in pointing them out, so good is the book; the illustration on page 240 is a little ambiguous with respect to its depiction of the mesoappendix and branches of the appendicular artery. Special problems in children are well covered, but these are spread across several chapters and one wonders whether a single chapter might have been worthwhile. Clinically, some problems remain; some patients develop diarrhoea following the use of even short segments of bowel and the longevity of the continence mechanism in continent diversion is problematic. Hopefully, the next edition of this book will address these issues.

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The Molecular Basis of Cancer

J. Mendelsohn, P. M. Howley, M. A. Israel and L. A. Liotta (eds). 284 × 218 mm. Pp. 574. Illustrated. 1995. Philadelphia, Pennsylvania: W. B. Saunders. £100.

This book is edited by four individuals, each with an international reputation in the field of molecular oncology. The author list of each chapter is, in itself, a roll-call of the major contibutors throughout the world in this field. The contents of the book should be mandatory reading for surgical trainees embarking on a period of research involving the application of molecular biological techniques to the detection, diagnosis, management and treatment of patients with malignant disease. The chapters work their way through the cell cycle, the concept of oncogenes, molecular genetics, viral carcinogenesis, multistep carcinogenesis and tumour suppressor genes, growth factors, signal transduction, metastasis, molecular diagnosis and the application of these processes to tumours of specific site and the molecular basis of treatment. Each section and chapter is outstanding in its field and it would be invidious to select any as being more noteworthy than the others. For surgeons I can particularly commend the first chapter on cell cycle and oncogenes, chapter 5 on tumour suppressor genes, chapter 9 on adhesion mechanisms and all chapters in Section III which discuss molecular abnormalities and specific malignancies. The important and emerging field of growth factors in malignancy, together with signal transduction mechanisms, is reviewed at an outstanding level, as are cellular immunity, gene therapy and monoclonal antibody therapy. The contributions by the king of metastasis research, Dr Lance Liotta are, in all respects, outstanding. Scientifically this book cannot be faulted

However I have to say that this is not a book that is going to find a place in the library of every surgical practitioner and it is unlikely to appeal to established consultants who do not have an interest in molecular oncology although, for those who feel the need to broaden their horizons on molecular diagnosis and therapy of malignant disease, this is an unparalleled reference. Those with an interest in the molecular basis of cancer as a research endeavour should make this volume available to their clinical research fellows. For that matter, senior clinicians and clinical academics with an interest in the field would do well to have this book for reference. To such individuals I cannot commend it highly enough, despite its price.

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Operative Surgery and Surgical Topics for the FRCS

K. M. Mokbel. 215 × 138 mm. Pp. 128. Illustrated. 1995. Dordrecht: Kluwer Academic Publishers Group. £12·95.

This is a pocket book containing a random collection of questions on operative surgery with model answers. Although it claims to cover the 40 commonest general surgical operations, it includes some procedures which are 'small print' for the general surgeon, e.g. surgery for meconium ileus, but omits other important ones, e.g. oesophagectomy and gastrectomy. Generally speaking the operative procedures are described well but where several techniques exist the one described is not always the most widely used, e.g. under inguinal hernia repair the Lichtenstein repair is described. Bold statements are sometimes made which are neither universally accepted nor reflect current practice, e.g. 'the incidence of wound infection is lower in laparoscopic compared to open appendicectomy', 'adjuvant cytotoxic chemotherapy is only indicated in premenopausal women with breast cancer', in anterior resection 'the rectum is mobilised by dividing the lateral ligaments and mesorectum'. The book also includes questions on popular exam topics such as audit, screening and medical statistics. Unfortunately, many of the answers in these sections are oversimplified, brief and not always technically correct. Despite these comments, candidates may find this book helpful in self assessment before the viva section of the CSIG examination. It is, however, by no means a comprehensive revision guide and there are numerous spelling mistakes throughout the text.

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Minimal Access Surgical Oncology

F. L. Greene and R. D. Rosin (eds). 253 × 193 mm. Pp. 197. Illustrated. 1995. Oxford: Radcliffe Medical Press. £75.

The advent of laparoscopic surgery some 5 years ago heralded a major change in surgical principles. Initial enthusiasm has been maintained for laparoscopic cholecystectomy, but for many other procedures there remains conflict as to the efficacy of minimal access techniques. This is perhaps no more true than in the management of cancer, as not only must one consider the surgical technique itself, but also the oncological principles involved.

Minimal Access Surgical Oncology is, therefore, a timely publication. The editors attempt to bring together all aspects of minimal access surgery relating to the diagnosis, staging and treatment of various tumours. On the whole, they succeed well The topics covered are wide ranging but at the same time pertinent to routine clinical practice. However, there is some reiteration between chapters and much of the text relates to oncological principles in general rather than minimal access implications. This is particularly true for the chapter on laparoscopic evaluation and resection of the spleen in cancer management. Furthermore, some of the topics covered are somewhat anecdotal, mainly because of overall limited experience with the techniques.

On the whole, this book is of great value and is a convenient up-to-date source of reference on minimal access surgery with respect to oncology. This is going to be a rapidly changing field and doubtless, as experience grows, further editions of this text will also change rapidly. This book is one of a series of texts dealing with the subject and, together, they will provide a complete overview for specialists in this field.

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Lower Extremity Vascular Disease

K. Ouriel (ed). 265 × 188 mm. Pp. 440. Illustrated. 1995. Philadelphia, Pennsylvania: W. B Saunders £99

This is yet another multiauthor offering which covers the field of vascular surgery. My first comment is that the title is not particularly accurate as the book has a section on aneurysm that includes thoracoabdominal and juxtarenal aneurysm. There are some notable exclusions, with neither detail concerning the diabetic foot nor mention of either the Miller cuff or Taylor patch. The book is very American and I must admit to finding its style fairly difficult to read. It provides reasonable coverage in some chapters, some of which are up to date. However, there are notable omissions of references (even American ones) in certain sections Unfortunately this volume does not appear to fill any gap in the market and is only of adequate topical interest; while it covers some recent advances, I suspect that subjects such as endoluminal grafting are changing so rapidly that any hardback book will struggle to keep up to date. To summarize, it is not a terrible book but it is just not good enough for me either to buy it or want it in my hospital library

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Current Controversy in Parathyroid Operation and Reoperation

G. Akerstrom. 260 × 180 mm. Pp. 222. Illustrated. 1995. Austin, Texas: R. G Landes. US $108.

A review of this book appeared in last month's issue It was written by M H. Wheeler, not M. H Walker as published The Journal apologizes to Mr Wheeler.

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Notices and announcements

31 January–2 February 1996
Arthroscopic Surgery
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

1 February 1996
9th International Congress on Breast Diseases
Houston, Texas, USA
Information: Office of Conference Services, UT M. D. Anderson Cancer Center, Postal Stop HMB 131, 1515 Holcombe Boulevard, Houston, Texas 77030-4095, USA

4–5 March 1996
Management Education for Clinicians
Edinburgh, UK
Information: Mrs C. Pottinger, Education, Audit and Research Department, Royal College of Physicians, 9 Queen Street, Edinburgh EH2 1JQ, UK

6–24 March 1996
FRCS Course
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

18–22 March 1996
An Update in Surgery for General Practitioners
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

22–23 March 1966
Neuroendocrine Tumor: New Biological and Clinical Aspects
Turin, Italy
Information: F. Orlandi and P. Paccotti, Clinica Medica Generale, Azienda Ospedaliera San Luigi Gonzaga, Regione Gonzole 10, 10043 Orbassano, Torino, Italy

22–24 March 1996
5th Biennial Meeting of the International Society for Applied Cardiovascular Biology
Manchester, UK
Information: M. G. Walker, Department of Vascular Surgery, Manchester Royal Infirmary, Manchester M13 9WL, UK

28–29 March 1996
Measurements in Wound Healing
Southampton, UK
Information: G. Kennedy, IPSM Meetings and Exhibitions, 4 Campleshon Road, York YO2 1PE, UK

31 March–3 April 1996
Trauma and Critical Care – 1996
Las Vegas, Nevada, USA
Information: Carol Williams, Trauma Department, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611, USA

3–5 April 1996
1st World Conference on the Prevention and Treatment of Caustic Oesophageal Burns in Children
Izmir, Turkey
Information: Professor O. Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, TR-35100 Izmir, Turkey

10–12 April 1996
96th Annual Congress of the Japan Surgical Society
Chiba, Japan
Information: K. Isono, Department of Surgery II, Chiba University School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260, Japan

11–12 April 1996
Endovascular Aortic Aneurysm Surgery
Nottingham, UK
Information. B. R. Hopkinson, Consultant Surgeon, University Hospital, Nottingham NG7 2UH, UK

14–18 April 1996
26th Biennial Congress of the International Society of University Colon and Rectal Surgeons
Lisbon, Portugal
Information: TOP Tours, Congress Department, R. Luciano Cordeiro, 116–1050 Lisboa, Portugal

5–9 May 1996
1st Congress of the World Association for Laser Therapy 'WALT'
Jerusalem, Israel
Information. World Association for LASER Therapy, c/o PO Box 50006, Tel Aviv 61500, Israel

7–10 May 1996
Research Methods in Surgery
London, UK
Information Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

12–15 May 1996
29th Annual Meeting of the Pacific Association of Pediatric Surgeons
Singapore
Information. Secretariat, Academy of Medicine, 16 College Road, Singapore 0316

20–22 May 1996
Trauma and Critical Care '96 - Point/Counterpoint XV
Boston, Massachusetts, USA
Information: Carol Williams, Trauma Department, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611, USA

22–25 May 1996
25th Meeting of the European Histamine Research Society
Antwerp, Belgium
Information: G. Van de Vyver, Department Geneeskunde, University of Antwerp, Universiteitsplein 1, B-2610 Antwerpen, Belgium

7 June 1996
Difficult and Controversial Issues in Vascular Surgery
Saltash, Cornwall, UK
Information: Mr S. Ashley, Vascular Surgical Unit, Derriford Hospital, Plymouth PL6 8DH, UK

12–15 June 1996
International Association of Pancreatology
Mannheim, Germany
Information. Mr A. L. Warshaw, IAP Secretary, Massachusetts General Hospital, 15 Parkman Street, WAC 336, Boston, Massachusetts 02114, USA

23–26 June 1996
4th International Congress of the European Association for Endoscopic Surgery
Trondheim, Norway
Information· Congress–Conference A/S, PO Box 7609 Skillebekk, N-0205 Oslo, Norway

26–29 June 1996
CAR'96 – Computer Assisted Radiology 10th International Symposium and Exhibition
Paris, France
Information· Professor H. U. Lemke, Technical University Berlin, Institute for Technical Informatics, Sekr. CG FR 3-3, Franklinstrasse 28–29, D-10587 Berlin, Germany

27–28 June 1996
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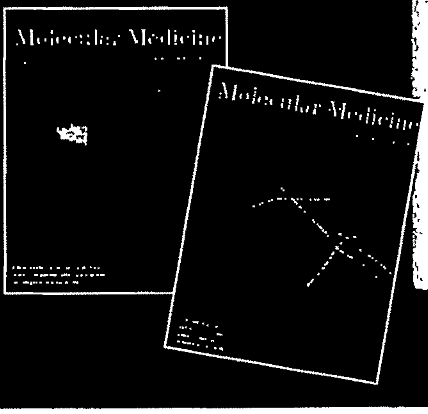

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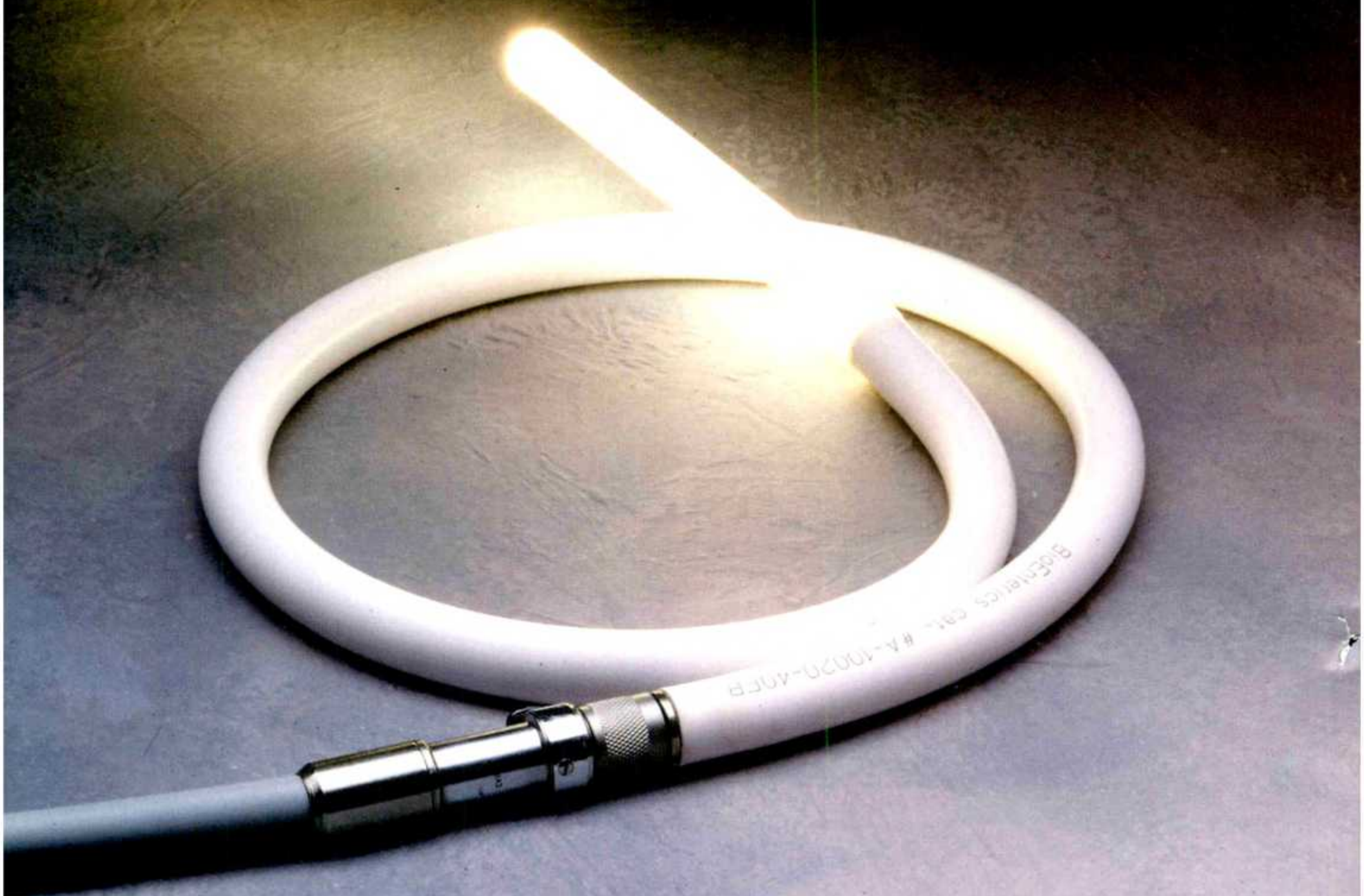

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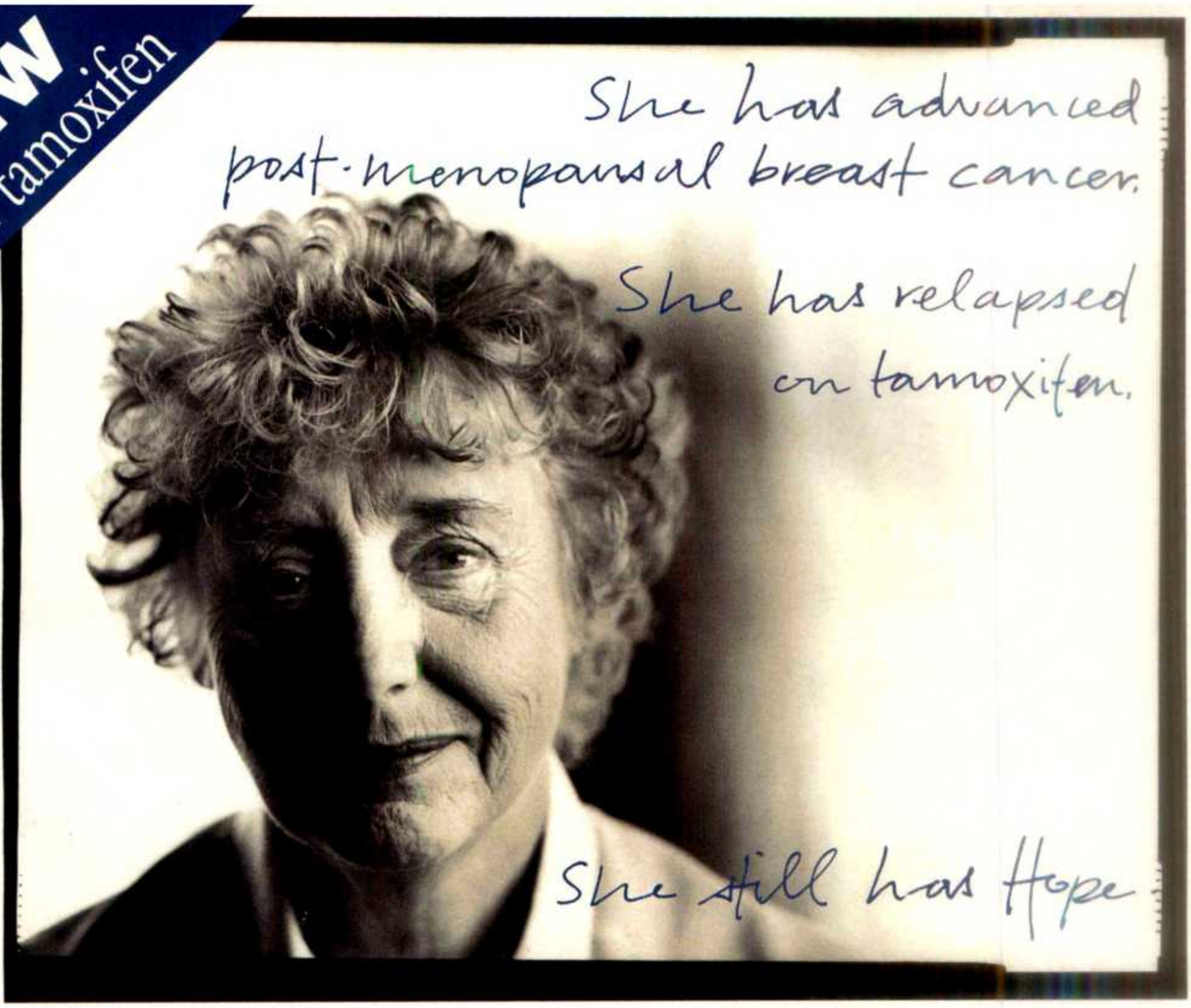
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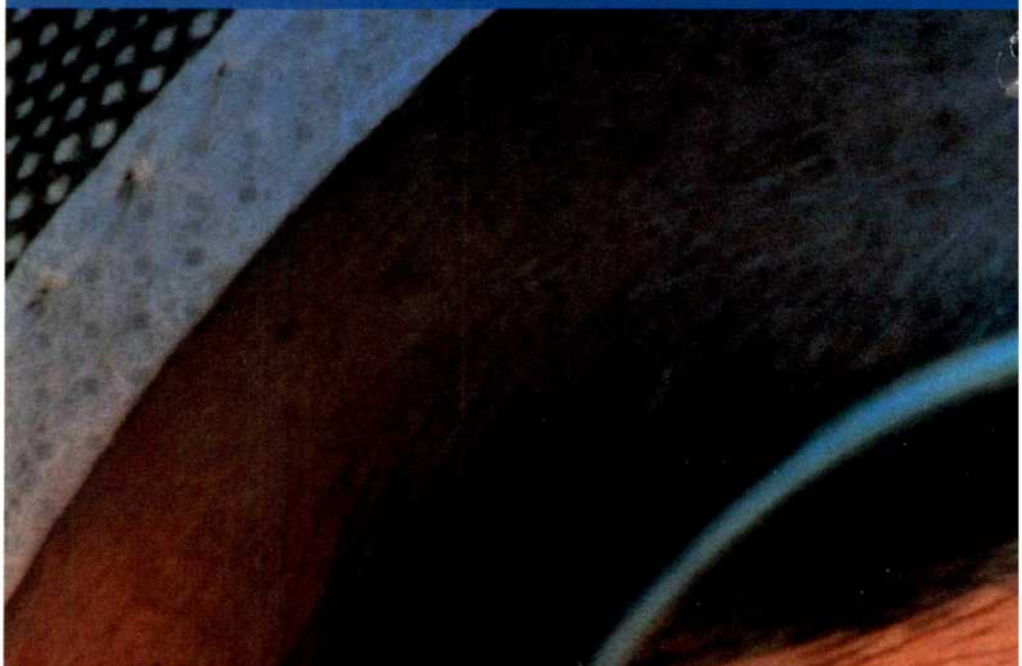

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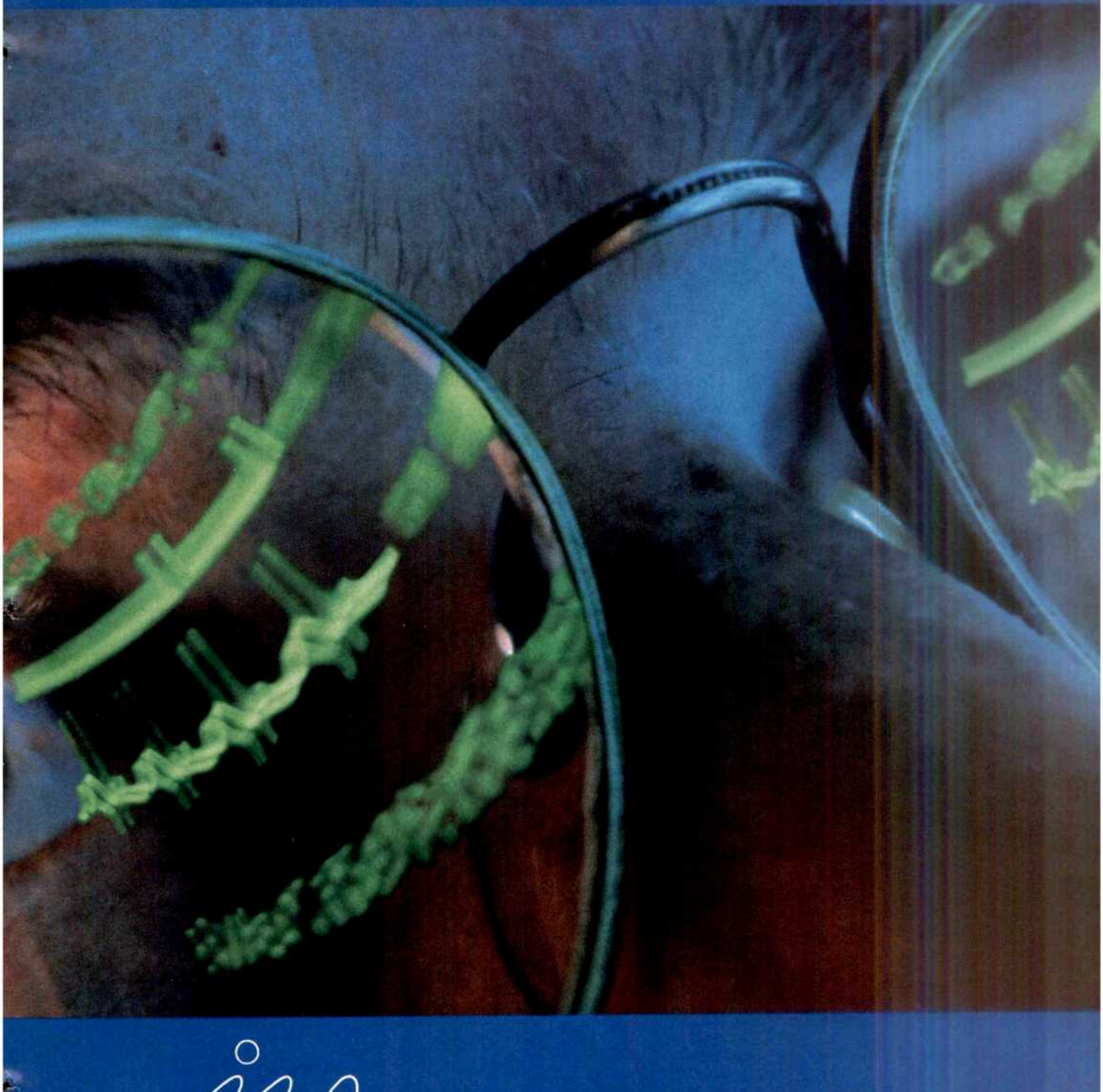

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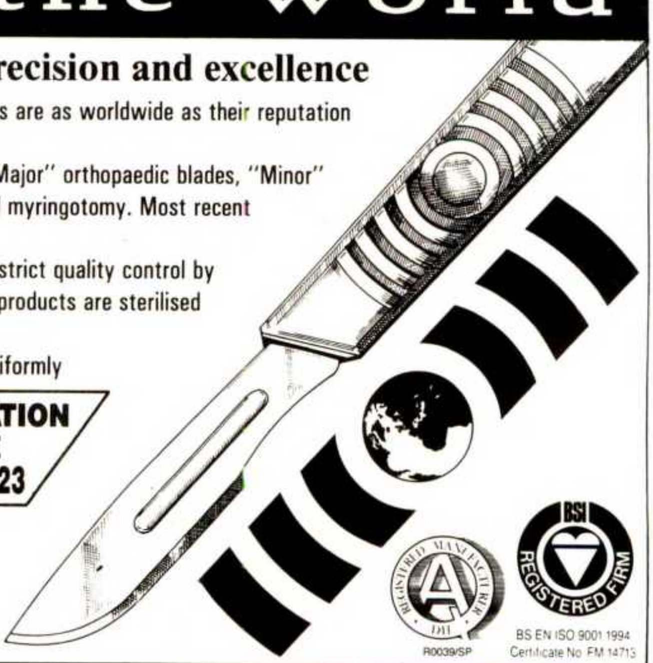

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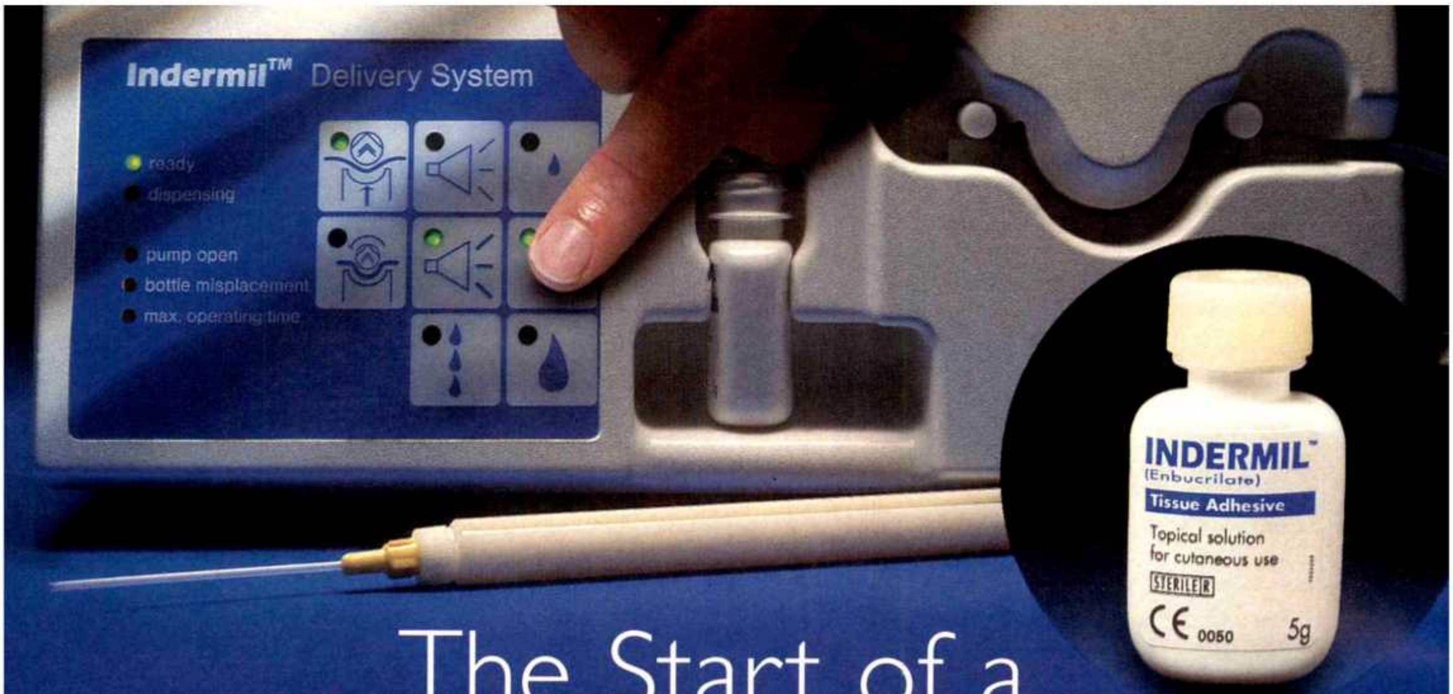

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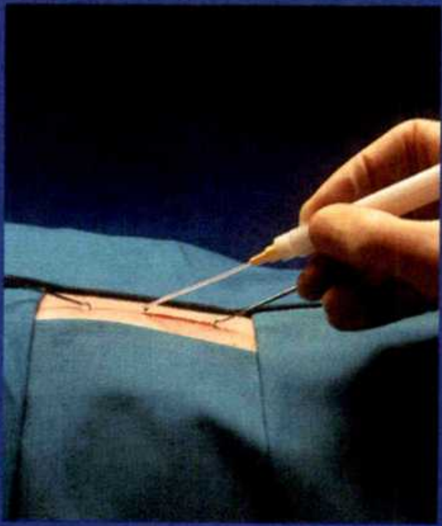

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Leading articles

The changing pattern of surgery

As the millennium approaches, the changes in our health care and health care systems seem to accelerate. Surgery and surgeons are no longer able to hide behind foreboding edifices and timeless traditions. Cost containment, 'best' practices, patients' rights, malpractice allegations and new technology are leaving many hospitals and surgeons bewildered and vulnerable to change with which they seem ill equipped to deal. While today's doctors seem able adeptly to embrace the challenges of organ transplantation, molecular biology and computer-assisted surgery, there is an alarming lack of understanding of such basic developments as day surgery[1], total quality management[2] and hospital-in-the-home[3]. No country has unlimited resources to throw into a poorly managed and inefficient surgical service; for far too long the emphasis has been on administrators to provide the solutions (usually in the form of increased funding) to maintain and enhance existing services. Surgeons have often believed their time and work too important to be spent at directing and implementing the changes needed to enhance the range and number of services their hospitals can offer. Yet there is increasing evidence worldwide that it is the clinicians who can, in reality, generate the needed improvements.

Day surgery is often seen as a rather unglamorous minor role for the serious surgeon, yet in many major institutions over 50 per cent of all procedures can now be conducted on a day-only basis[4]. This is no mean feat, requiring not only state-of-the-art equipment and considerable surgical skill, but also dedicated, specially trained, nursing and anaesthetic staff, a flexible admission policy and informed home nursing support. Surgeons need to learn often quite different approaches to the traditional operations. In Adelaide, until quite recently, repair of an inguinal hernia meant a general anaesthetic, 3–4 days in hospital and often a prolonged period off work. By altering surgeons' and patients' attitudes to the operation, it is now more accepted that such surgery should be performed on a same-day basis, conducted under local anaesthesia with adequate and aggressive postoperative pain management[5]. Patients, previously often sceptical or even frankly resentful of such treatment, now express high levels of satisfaction with this approach. In appropriately selected patients, the performance of laparoscopic cholecystectomy on a day-surgery basis is a very real option, which was unimaginable even 5 years ago[6]. Centres with active day surgical units report 30-day readmission rates of less than 2 per cent. Failure-to-discharge rates may be higher but, provided beds are available for unplanned admissions, it is possible to ensure that an even broader range of patients is reached. Appropriate at-home nursing, responsible adult supervision, telephone communication and an acceptable distance of the home from the surgical centre are needed if optimal acceptance is to be achieved and disasters avoided[5].

As more operating is moved to day-surgery facilities, so the character of general inpatient theatre lists must change. Proportionally more major, more invasive surgery will be concentrated in the general theatre area. Surgeons, anaesthetists and nursing staff may be exposed to more stressful and prolonged sessions. Inpatient facilities face an increasing number of patients who require intensive care and high-dependency beds; wards that were once the home of the patient convalescing after varicose vein or gallbladder surgery are being occupied by an increasing proportion of 'heavy' patients.

For many surgeons, politicians and patients, a hospital's or clinician's importance and relevance is measured in the number of beds 'owned' or controlled. However, beds are a simplistic and basically meaningless measure of activity; it is far more important to consider surgical output and complexity rather than 'real estate'. While 'output' has a rather industrial connotation, there is much surgeons can learn from modern industrial practice. Principles of Total Quality Control and Just In Time[2,7] have as much validity in the modern hospital as in the car plants of Japan. Careful documentation of all operative procedures, preoperative and postoperative care, and associated costs can, with the aid of computer databases, be used critically by the clinician to trigger important improvements in treatment and surgical practice. Well organized investigational services and patient ambulatory support services mean that patients may be admitted on the day of surgery rather than undergoing unnecessary hospitalization for investigation and preparation[8].

Are there dangers in this brave new world of changing surgical practice? Undergraduate teaching may be a victim, unless surgeons and students adapt to the changing environment. Long teaching ward rounds with osmotic learning are from a past era; students need structured teaching in settings like preadmission clinics, day-surgery units or ambulatory care centres. The opportunity of exposing a student to the presenting complaint, the investigations and the surgical procedure, all on the same day, offers considerable educational potential. To grasp such an opportunity may require a radical shift in approach for many tradition-bound surgeons, but failure to attempt to meet this challenge is not acceptable.

How may surgery adapt to the forces of decreasing health budgets, increasing patient expectations and ageing populations? New approaches must be developed by surgeons, who should not blame administrators or governments if they are not themselves prepared to participate in the implementation of such new approaches. For some same-day admissions, day-surgery and preadmission clinics may seem of obvious benefit but, in addition, we must develop critical audit systems and relevant clinical pathways[9], approaches viewed by many of our clinical colleagues as intrusions into their autonomy. The future does not promise an easy time for surgeons uncomfortable with change but, for those able to accept the challenge, it will be not only exciting but also of vital importance to the communities they serve and the students they teach.

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Renal transplantation from non-heart-beating donors

There continues to be a serious shortage of suitable kidneys for transplantation in Great Britain and Ireland. Over 5000 patients are now on the United Kingdom Transplant Service kidney transplant waiting list but during 1994 only 1750 kidney transplants were performed. In recent years heart-beating, brain stem-dead, cadaveric donors have been the main source of kidneys for transplantation, but the falling death rates from both road traffic accidents and intracerebral haemorrhage[1] suggest that it will not be possible to increase the supply of organs by concentrating on this traditional source. Because of this there has been renewed interest in the non-heart-beating (NHB) donor as a source of kidneys.

The biggest source of NHB donor kidneys is from patients who suffer irreversible cardiorespiratory arrest following myocardial infarction and are dead on arrival at hospital[2,3]. Patients who die from a sudden intracerebral catastrophe in the ward setting may also be suitable, and at least one transplant unit has used kidneys from hospice-based patients who have died from primary brain tumours[4]. It should be emphasized that death must be pronounced before NHB donation can even be considered; this is, therefore, a totally different situation from the elective ventilation of potential organ donors before death has occurred. Certain basic criteria must be met for NHB donation to proceed. The patient should be under 60 years of age and have no history of renal impairment, uncontrolled hypertension, insulin dependent diabetes, systemic sepsis or malignancy (except primary central nervous system tumour). The total acceptable duration of circulatory arrest, and therefore renal warm ischaemia, is debatable but is of the order of 30–40 min[2,3]. After death has been pronounced, external cardiac massage and ventilation with 100 per cent oxygen may be continued in an attempt to limit the degree of renal ischaemia. This may be carried out manually but highly effective mechanical devices which perform cardiac massage and mechanical ventilation are available. The next requirement is to achieve rapid *in situ* cooling of the kidneys and a number of techniques are available for this. The usual method is to insert a double-balloon triple-lumen catheter into the aorta to isolate the renal circulation[5]. The catheter is introduced via a femoral artery cut-down in the groin. Inflation of the balloons occludes the aorta at its bifurcation and at the level of the diaphragm. The isolated renal circulation is then selectively perfused with an appropriate preservative solution at 4°C and the system is vented by a Foley catheter placed in the femoral vein. Arrangements can then be made for transfer of the donor to an operating theatre where a formal donor nephrectomy operation is performed. Other techniques for *in situ* organ cooling are intraperitoneal lavage using cold Ringer lactate solution[6] and total body cooling by extracorporeal cardiopulmonary bypass[7].

A number of groups in the UK and Europe have published encouraging early graft survival data on NHB donor kidneys but, in general, the results have not been quite as good as those of heart-beating cadaveric donor transplants. Graft survival figures for 1 and 3 years range from 73 to 80 per cent and 60 to 74 per cent respectively[3,8–10]. In the medium term at least, NHB donor kidneys can achieve a good level of function with, for example, a mean serum creatinine concentration of 174 μmol/l at 12 months of follow-up[3]. Nonetheless, delayed graft function is particularly common after NHB donor transplantation; rates range from 60 per cent[3] to 100 per cent[2,10] and this may explain the slightly inferior graft survival figures[11]. The rate of permanent non-function in NHB donor kidneys is also relatively high at 8 to 15 per cent[3,8,10]. This is a consequence of irreversible warm ischaemic renal damage and a rapid reliable preoperative test to predict tissue viability is needed to avoid the transplantation of kidneys that are unlikely to function. Even higher levels of primary non-function have been recorded for NHB donor kidneys taken from hospice patients dying from primary cerebral tumours[4]. In this situation, families were given time to be with the deceased relative before the donors were taken to the mortuary for kidney removal. In the absence of cardiac massage, artificial ventilation and *in situ* cooling, these kidneys suffer a greater degree of warm ischaemia than those from acute donors who die in the accident department, and it is not surprising that the results are much worse.

Perhaps the most interesting and difficult questions surrounding the use of NHB donation are legal and ethical. The principle issue is: can *in situ* organ cooling be justified before permission is sought from the family of the deceased? In cases of sudden death the next-of-kin is not always quickly available and even a short delay can lead to a loss of suitable organs. In Leicester, *in situ* kidney perfusion has occasionally been performed before consultation with relatives. This has been considered an acceptable practice because the femoral cut-down procedure disturbs the body of the deceased very little. The approval of both the local coroner and hospital ethical committee has been obtained and the protocol published in the local press without any objections being raised. Written consent from relatives is still required, however, before organ retrieval can be performed. Careful consultation and planning of this sort is essential to avoid a mistaken public perception of what we are trying to achieve. It is well known that negative publicity can dramatically decrease the rate of organ donation.

NHB donor kidneys are an important source of additional organs, accounting for over 30 per cent of some kidney transplant programmes[10]. Several problems still need to be solved but the early results are encouraging enough to support continued development in this area.

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Review

Local recurrence after breast-conserving surgery for breast cancer

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Local recurrence following breast-conserving surgery for breast cancer is a significant failure of local treatment. This article reviews the mechanisms, risk factors and overall significance of such local recurrence. The presence of disease at excision margins, an extensive intraduct component, lymphatic vessel invasion, tumour grade and tumour size are currently the best predictors of risk for local recurrence. Early local recurrence is due to residual disease and is associated with both decreased distant disease-free survival and overall survival; it appears to reflect aggressive biological characteristics of the primary tumour. The importance of adequate local treatment for breast cancer is discussed.

Breast-conserving surgery involves excision of the primary tumour with a margin of normal surrounding tissue, followed by administration of postoperative radiotherapy to the breast. The aim is to achieve maximal cosmesis and minimal psychological morbidity, without compromising overall survival. To date, seven randomized trials have compared mastectomy with breast-conserving surgery plus radiotherapy. One trial failed because the constraints of informed consent resulted in poor patient accrual[1]. Six trials have published medium- to long-term results[2–7]. These trials, with follow-up ranging from 6 to 13 years, have demonstrated no significant difference in overall survival and distant disease-free survival between the various treatment arms (*Table 1*). Five randomized trials have compared breast-conserving surgery alone with breast-conserving surgery plus adjuvant radiotherapy[8–11]. With follow-up ranging from 4 to 9 years, no significant difference in overall survival or distant disease-free survival between the various treatment arms has been reported. However, highly significant differences in the incidence of local recurrence were observed in all these trials (*Table 2*).

Local recurrence in the breast potentially undermines all the aims of breast-conserving surgery. Psychologically, a patient will lose confidence in the treatment, suffer the anxiety of cancer recurrence and may face the prospect of undergoing mastectomy. Further surgery means that the cosmetic benefits of breast conservation are lost. In addition, when patients with local recurrence are analysed separately, associations between such recurrence and shorter distant disease-free and overall survival have been reported[10,12–14]. The significance of these associations is the subject of considerable debate. In the present article the problem of local recurrence following breast-conserving surgery, its mechanisms, risk factors and relationship to distant disease and overall survival are reviewed.

Mechanism of local recurrence

Local recurrence is due to residual disease left in the breast at the time of surgery for the primary tumour or to a second primary tumour developing in the breast. Throughout the evolution of surgery for breast cancer the possibility of leaving behind residual disease has been a cause for concern. All trials of breast-conserving surgery have, therefore, adopted measures to ensure complete local excision of the tumour. This practice was supported by laboratory-based studies involving serial sectioning or simulated wide local excision of tumours in mastectomy specimens. Rosen *et al.*[15] performed quadrantectomy or wide local excision with a 2-cm margin in 203 mastectomy specimens. Residual microscopic invasive or *in situ* disease was found in 26 per cent of specimens containing tumours less than 2 cm in diameter and in 38 per cent of those containing tumours larger than 2 cm. A subsequent study by Holland *et al.*[16] analysed mastectomy specimens by serial sectioning from 282 patients who would theoretically have been suitable for breast-conserving surgery. Residual invasive or *in situ* disease was found in 59 per cent of specimens at a distance of 1 cm, in 42 per cent at a distance of 2 cm, in 17 per cent at a distance of 3 cm and in 10 per cent at a distance of 4 cm from the macroscopic edge of the tumour. In these studies, approximately one-third to one-half of the residual disease detected was invasive. These results have accurately predicted the incidence of local recurrence observed in clinical trials in which radiotherapy was not administered. In the lumpectomy-only arm of the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-06 trial, in which a 1-cm clearance margin was taken around the tumour, the local recurrence rate was 53 per cent at 10 years[17]. In the quadrantectomy-only arm of the Milan III trial, in which a 2–3 cm clearance might be expected, the local recurrence rate was 8·8 per cent at 3 years[8].

There is strong support for the view that a large majority of local recurrences represent residual disease. In an analysis of the patients having lumpectomy in the NSABP B-06 trial, all 110 local recurrences occurred in or close to the quadrant of the original tumour. The histological types and grades were identical in 86 per cent[18]. In the Milan study of patients treated by quadrantectomy, 60 per cent of local recurrences were of the same histological type and 79 per cent occurred at or very close to the site of previous excision[12]. Kurtz *et al.*[13] reported that 86 per cent of local recurrences occurring within 5 years affected the site of previous wide local

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Table 1 Randomized trials of breast-conserving surgery plus radiotherapy *versus* mastectomy

Trial	Randomization	No. of patients	Tumour size (cm)	Length of follow-up (years)	Overall survival rate (%)	Distant disease-free survival rate (%)
Milan I (1973–1980)	Quadrantectomy plus radiotherapy	352	≤2	13	71	n.s.
	versus					
	mastectomy	349			69	
NSABP B-06 (1976–1984)	Lumpectomy plus radiotherapy	625	≤4	9	69	60
	versus					
	mastectomy	586			68	63
World Health Organization (1972–1980)	Lumpectomy plus radiotherapy	88	≤2	10	79	n.s.
	versus					
	mastectomy	91			80	
National Cancer Institute (1979–1987)	Lumpectomy plus radiotherapy	121	≤5	10	77	n.s.
	versus					
	mastectomy	116			75	
EORTC (1980–1986)	Lumpectomy plus radiotherapy	452	≤5	8	n.s.	n.s.
	versus					
	mastectomy	426				
Danish (1983–1989)	Lumpectomy plus radiotherapy	430	—	6	79	n.s.
	versus					
	mastectomy	429	—		82	

NSABP, National Surgical Adjuvant Breast and Bowel Project; EORTC, European Organisation for Research and Treatment of Cancer; n.s., no significant difference (actual values not available)

Table 2 Randomized trials of breast-conserving surgery with or without radiotherapy

Trial	Randomization	No. of patients	Tumour size (cm)	Length of follow-up (years)	Overall survival rate (%)	Distant disease-free survival rate (%)	Local recurrence rate (%)
Milan III (1987–1989)	Quadrantectomy	273	<2·5	4	n.s.	n.s	9
	versus						
	quadrantectomy plus radiotherapy	294					0†
NSABP B-06 (1976–1984)	Lumpectomy	632	≤4	9	68	59	43
	versus						
	lumpectomy plus radiotherapy	625			69	60	12†
Ontario (1984–1989)	Lumpectomy	396	≤4	5	86	n.a.	30
	versus						
	lumpectomy plus radiotherapy	403			88		8†
Swedish (1981–1988)	Sector resection	197	≤2	5	90	87	18
	versus						
	sector resection plus radiotherapy	184			91	90	2†
Scottish* (1985–1989)	Lumpectomy	294	<4	6	82	64	29
	versus						
	lumpectomy plus radiotherapy	291			83	80	6†

NSABP, National Surgical Adjuvant Breast and Bowel Project; n.s., no significant difference (actual values not available); n.a., data not available. *Unpublished results. †$P<0{\cdot}05$ *versus* treatment without radiotherapy

excision. Only 75 per cent of local recurrences that occurred between 5 and 10 years and 36 per cent of those presenting after 10 years affected the site of previous excision. In a study of 990 patients treated by lumpectomy with a median follow-up of over 5 years, Haffty *et al.*[19] analysed local recurrences in terms of location, histology and DNA flow cytometry. Of 80 recurrences, 59 per cent were classified as representing residual disease and 41 per cent as new primary tumours. The time to local recurrence was significantly shorter in patients with local recurrence secondary to residual disease (3·6 years) than in those thought to have a second primary cancer (5·7 years). In the NSABP B-06 trial, the annual rate of local recurrence in the lumpectomy-only arm decreased from 8·5 per cent during the first 3 years of follow-up to 4·6 per cent in years 4–9, whereas in the lumpectomy plus radiotherapy arm the rate of local recurrence was constant at 1·4 per cent[14]. It appears, therefore, that much early local recurrence should be attributed to residual disease. The cause of late local recurrence or recurrence in the breast distant from the site of previous excision is less clear.

It is difficult to distinguish between local recurrence due to residual disease from that due to a new primary tumour. In the Milan II trial, which compared quadrantectomy plus radiotherapy with tumorectomy plus radiotherapy, local recurrence was defined as tumour relapse within 3 cm of the surgical scar[9,20]. Recurrence in the breast beyond this was defined as a new primary lesion. A significant difference was observed in the incidences of local recurrence, confirming that a wider excision margin reduces the risk, but there was no significant difference in the incidences of new primaries. In addition, the incidence of contralateral tumours was similar for both quadrantectomy and tumorectomy groups, and was greater than that of new primary lesions in the ipsilateral breast. Thus the incidence of new primaries appears no greater than expected. It might even be less, suggesting that radiotherapy may protect the breast from developing a second primary breast cancer.

Assessing margins of excision

Various methods for assessing the completeness of excision have been devised. Patients with evidence of incomplete excision can be selected for subsequent wider excision or mastectomy. In the NSABP B-06 trial, margins were assessed using the technique of India ink staining. This involved coating the lumpectomy specimen in ink and obtaining sections from the anterior, posterior, medial and lateral aspects of the specimen. These were blocked sagitally, and excision was deemed incomplete only when tumour had been transected by the inked margin. In this trial, between 12 and 20 blocks were taken from each specimen. In all, 10 per cent of patients were shown to have involved margins and subsequently underwent mastectomy. Twenty-nine per cent of mastectomy specimens contained residual disease. However, review of the histological slides of patients thought to have margin involvement demonstrated a lack of consensus among different pathologists in 69 per cent of cases. Where agreement was reached, residual disease was found in 67 per cent of mastectomy specimens[18]. Despite this policy, local recurrence rates in this trial were high. This method of margin assessment appears to underestimate markedly the true incidence of residual disease after lumpectomy.

Frazier *et al.*[21] used the same criteria as in the NSABP B-06 trial to assess margins. In this study of 87 patients, who underwent diagnostic excision biopsy for breast cancer, 75 subsequently opted for mastectomy regardless of margin status and 12, who wished breast conservation, had re-excision performed for involved margins. Original margin status and incidence of residual disease in the breast could therefore be compared. Re-excision and mastectomy specimens contained residual tumour in 52 per cent of those with involved margins, in 32 per cent of those with uninvolved but close margins and in 26 per cent of those with clear margins[21]. Close margins have been variably defined as tumour found within 1, 2 or 5 mm from the inked surface[22–24]. Gwin *et al.*[25] demonstrated residual disease in 65 per cent of patients with a positive margin, in 23 per cent of those with a close margin and in 45 per cent where the margin status was unknown[25]. Local recurrence rates at 5 years have been reported to be between 2 and 21 per cent for patients with positive margins and between 4 and 11 per cent for those with close margins[23,24]. In two studies no local recurrences have been recorded at 5 years for patients with negative margins after initial surgery or re-excision[22,24]. However, in one of these studies[24] over 50 per cent of patients had positive margins initially and so required re-excision.

Other methods of assessing the margin of excision include taking multiple biopsies from the cavity remaining in the breast following lumpectomy. Umpleby and colleagues[26] demonstrated residual disease in 25 per cent of patients with this method. Alternatively, a thin shaving may be taken from the entire cavity wall. In a study[27] using this technique, where the cavity wall shaving was extensively blocked and sectioned, residual disease was found in 38 per cent of patients. Detailed analysis of resection margins thus increases detection of incomplete excision. However, assessing completeness of excision is difficult, labour intensive, and current methods appear flawed. It is, therefore, important to establish the factors that might accurately predict patients at risk of developing local recurrence.

Risk factors for local recurrence

Extensive intraduct component

The presence of an extensive intraduct component (EIC) within the tumour was proposed as a risk factor for local recurrence by the Joint Centre for Radiation Therapy (JCRT). EIC is defined as present if an infiltrating ductal carcinoma has both predominant intraduct carcinoma within the tumour (also specified as greater than 25 per cent) and intraduct carcinoma in sections of grossly normal adjacent breast tissue. Vicini *et al.*[28] demonstrated in 584 patients treated by local excision and radiotherapy that 5-year local recurrence rates were 21 per cent in 166 patients who had EIC and only 6 per cent in 418 without the component. Patients with EIC accounted for 58 per cent of all local recurrences[28]. In an analysis of the series of mastectomy specimens previously reported to show residual disease at varying distances from the macroscopic edge of the tumour, Holland *et al.*[16,29] looked specifically at the influence of EIC on their observations. Of 66 specimens in which the tumour exhibited EIC, the incidence of residual disease was significantly greater when compared with that in 151 specimens that did not show the component. Further analysis showed that this difference was predominantly due to a greater incidence of residual intraduct carcinoma in patients with EIC. EIC has no effect on the incidence of recurrent tumour within the breast distant from the site of previous excision[30,31].

The significance of EIC in relation to the incidence of local recurrence has been analysed in some of the randomized trials of breast-conserving surgery. EIC was found to be a highly significant predictor for local recurrence in the Milan II trial, particularly in the tumorectomy group in which local recurrence was noted in 28 per cent of patients who had EIC[20] EIC accounted for 18 per cent of all local recurrences in an overview of patients treated by quadrantectomy[12]. No association between local recurrence and EIC was found in the NSABP B-06 trial; this is the major exception to the consensus that EIC is an important predictor of local recurrence[17]. An important difference between these trials was the fact that 10 per cent of patients in the NSABP B-06 trial had mastectomy because of positive resection margins but were analysed in their original randomized treatment arm. In addition, the reported incidence of tumours with EIC varied. It was stated as being present in 13 per cent of patients in the NSABP B-06 trial but in only 6·7 per cent of those in the Milan trials[9,32]. In the JCRT study[28], EIC was present in 28 per cent of patients and in the pathological study by Holland *et al.*[29] it was present in 30 per cent of specimens. Thus definition and interpretation of what constitutes EIC appear to vary considerably between different institutions.

The type of intraduct carcinoma present may be important. Lindley and co-workers[33] found that comedo-type intraduct carcinoma was associated with a local recurrence rate of 50 per cent. This is in accordance with studies of pure ductal carcinoma *in situ* (DCIS). In the NSABP protocol B-17 trial of breast-conserving surgery for DCIS, comedo necrosis and involved margins were the only independent predictors of local recurrence[34]. Schwartz *et al.*[35] observed among 70 patients who had wide excision of DCIS that there were 11 recurrences at 4 years. All but one patient had comedo DCIS as the primary lesion. The presence of EIC can frequently be predicted by identifying typical patterns of microcalcifications on preoperative mammograms[36].

Lymphatic vessel invasion

Another risk factor for local recurrence is the presence of lymphatic vessel invasion. This was found significantly to predict for local recurrence in the Milan overview of quadrantectomy[12]. It was found in only 6·5 per cent of patients, but 24 per cent of all local recurrences occurred in this group. In the NSABP B-06 trial, lymphatic invasion was associated with a significantly increased risk of local recurrence in patients undergoing breast-conserving surgery. This association was noted at 3 years' follow-up but lost statistical significance with longer follow-up[17,18]. Other studies have shown invasion into lymphatic or blood vessels to be important. In an analysis of 518 patients treated at the Institute Curie, 6 per cent had endolymphatic extension of tumour and 13 per cent of all local recurrences occurred in this group[37]. Locker *et al.*[38] found endolymphatic invasion in 24 per cent of tumours, which strongly correlated with local recurrence, and this association was most pronounced in the first 2 years of follow-up.

Histological type and grade

Other pathological factors reported to be significant predictors for local recurrence include histological type and histological grade of the tumour. It was thought initially that lobular carcinoma would not be suitable for breast-conserving surgery due to its association with multicentricity. Studies have shown, however, that local recurrence rates comparable with those for ductal carcinoma can be achieved[39,40]. Lobular carcinoma was not associated with an increased risk of local recurrence in the Milan[12] or NSABP[17] conservation trials. The importance of histological grade varies between studies and with the type of grading system used. The NSABP B-06 trial[17] reported that nuclear grade was a significant predictor for time to local recurrence in node-positive patients after long follow-up. When the Bloom and Richardson classification[41] of tumour grade has been used, the risk of local recurrence has generally been found to increase with increasing grade[33,38,42].

Tumour size

Tumour size has been reported to be a predictor for local recurrence in most studies. Local recurrence was significantly more common in patients with pathological tumour size greater than 2 cm than in those with smaller tumours in the NSABP B-06, EORTC and Milan trials, particularly in those patients who did not receive radiotherapy[6,12,14,17]. Other investigators have made similar observations in non-randomized studies[38]. Some have also found difficulty in obtaining pathologically clear margins of resection in patients with large tumours[24,25]. Interestingly, the incidence of widespread microscopic disease around the tumour was not related to tumour size in Holland *et al.*'s series of sectioned mastectomy specimens[16], although Rosen *et al.*[15] demonstrated that large tumour size was associated with multifocal disease. It is, therefore, probable that tumour size assumes importance when surgical clearance is limited for cosmetic reasons.

Age

Young age has also generally been found to correlate with increased risk of local recurrence. Patients younger than 35 years appear to be at particularly high risk. In the Milan overview of quadrantectomy[12], Cox regression analysis showed that young women were significantly more likely to develop local recurrence. However, associations have also been reported between young age and multicentricity, multifocality, vascular invasion, high tumour grade and EIC[43–46]. Young age is generally not found to be independently significant when these factors are taken into account.

The presence of EIC, lymphatic invasion, poor histological grade, large tumour size and young age have, therefore, all been implicated with increased risk of local recurrence. Locker *et al.*[38] have reported that a combination of risk factors may be useful in predicting this risk.

Significance of local recurrence

It has been argued that local recurrence is of no significance and that attention given to it in the literature is exaggerated[47,48]. This opinion is based on the fact that, in the most recent trials, local recurrence rates are low. This is attributed to the more widespread use of chemoendocrine therapy which, as might have been expected, reduces the incidence of local recurrence[2,6,12,17,49]. The results of the breast-conservation trials (*Tables 1* and *2*) show that overall survival and the risk of developing distant recurrence following surgery for breast cancer have no statistically significant association with either the extent of the surgical procedure or the administration of postoperative radiotherapy. However, when patients who develop local recurrence are analysed separately and compared with those without local recurrence, clear differences in both distant disease-free survival and overall survival are observed.

In the NSABP B-06 study, a Cox regression model analysis of local recurrence demonstrated that patients who developed local recurrence were 3·41 times more likely to develop distant disease[14]. In addition, at 1-, 2- or 5-year cut-offs, patients who had early local relapse were significantly more likely to develop distant disease than those who experienced this event late. A similar analysis was performed on results from the Ontario randomized trial of breast-conserving surgery with or without radiotherapy[10]. This showed that the relative risks of both distant disease and overall mortality were more than doubled in patients who had local recurrence (2·11 and 2·18 respectively). Again, patients who developed local recurrence within 1 year were at significantly higher risk than those in whom local recurrence occurred late. Applied to data from the Milan breast-conservation trials and a large group of non-randomized patients treated by quadrantectomy, Cox regression model analysis has shown the risk for distant disease to be 4·62 times greater in those who had local recurrence. In this trial the risk was six times greater if local recurrence occurred within 1 year[12]. In a non-randomized study of 1593 patients treated by breast-conserving surgery and radiotherapy with follow-up of 11 years, Kurtz *et al.*[13] showed that survival relative to the onset of local recurrence varied significantly and that those who developed local recurrence after 5 years had the same overall survival as those who were disease free. In the group of patients who had local recurrence analysed in terms of location, histology and DNA flow cytometry by Haffty *et al.*[19], the 5-year survival rate following breast recurrence varied from 89 per cent in those with second primaries to 36 per cent in those with recurrence due to residual disease. Early local recurrence appears, therefore, to be strongly associated with the development of distant disease.

The evidence implicating local recurrence with the development of disseminated disease does not, however, translate into significant differences in distant disease-free or overall survival between the treatment arms of randomized trials. This is surprising, considering the large differences in the incidence of local recurrence that were observed. In the NSABP B-06 trial the cumulative incidence of local recurrence at 10 years was 53 per cent in the lumpectomy-only group, compared with 12 per cent in the group that received adjuvant radiotherapy. However, there was no significant difference in the incidence of distant disease or overall survival between these groups[17]. Four other trials of conservation surgery with or without radiotherapy have supported this finding, although non-significant differences in distant disease-free survival have been reported in favour of patients who received radiotherapy (*Table 2*). Preventing local recurrence in the breast by performing a mastectomy has not been shown to reduce the incidence of distant disease or to improve survival (*Table 1*).

Arguments have been postulated to explain this apparent inconsistency. First, if local recurrence does cause distant disease, predicted differences in outcome would be small, and the numbers of patients and duration of follow-up in each of these trials may not be sufficient to detect this. This argument is supported by the long-term results in patients undergoing adjuvant radiotherapy following mastectomy, in which a survival benefit conferred by radiotherapy was seen only after 15 years[50]. It has been suggested that local recurrence after breast-conserving surgery is a marker for distant disease rather than the cause for it[14]. The risk of developing distant disease would thus be predetermined before treatment, with local recurrence being a manifestation of this risk.

There is a need to discriminate between risk factors for local recurrence and risk factors for both local recurrence and distant disease, as not all patients who develop local recurrence are at increased risk of distant disease. EIC, while strongly predicting residual disease and local recurrence, does not (as might have been predicted) correlate with distant disease-free or overall survival[28,30,31]. Lymphatic vessel invasion and tumour grade, however, correlate with local recurrence, distant disease and overall survival[12,37,38,51,52].

Conclusions

Local recurrence and its predisposing factors are important and deserve detailed consideration in the selection and management of patients suitable for breast-conserving surgery. Recurrence in the breast which occurs early and close to the site of previous excision can be attributed to residual disease. Assessing margins of surgical excision is useful and can provide an indication of the risk of developing local recurrence. Re-excision based on positive margins has been shown to decrease the incidence of local recurrence. Tumour factors associated with an increased risk of local recurrence require better definition. However, EIC, lymphatic vessel invasion, tumour grade and tumour size should be taken into account along with margin status in determining optimal surgical treatment At present, the decision to offer wider excision is based on pragmatic appraisal of these factors, with the safeguard of radiotherapy. The results of trials assessing selection criteria for administering adjuvant radiotherapy to patients undergoing breast-conserving surgery are awaited.

Early local recurrence is significantly associated with poor distant disease-free survival. This appears to reflect inherent aggressive biological characteristics of the primary tumour. However, longer follow-up in randomized trials is required to eliminate the possibility of a direct causal effect. Appropriate selection of patients for surgical treatment of breast cancer is vitally important. Until further data become available, patients undergoing breast-conserving surgery should receive adjuvant postoperative radiotherapy. When practising breast-conserving surgery, its aims must be remembered; it is imperative that these are not forfeited through inadequate local treatment.

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Review

Prognostic significance and surgical management of lymph node metastasis in gastric cancer

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Regional lymph node metastasis is a critical prognostic factor in gastric cancer, and extended lymph node dissection and routine microscopic examination of all resected nodes could potentially provide accurate information regarding lymph node status. On the other hand, the therapeutic value of extended lymph node dissection is controversial. While retrospective and prospective non-randomized comparative studies have shown that extended lymph node dissection significantly improves the survival rate, two prospective randomized trials have failed to demonstrate the efficacy of extended dissection, although the number of patients in these studies was limited. There is a further, ongoing, trial involving a larger series of patients; the final results of this study should help to determine whether extended lymph node dissection is of therapeutic or merely prognostic value in gastric cancer.

The mortality rate from gastric cancer has been decreasing worldwide[1]. In Japan, although gastric cancer is the leading cause of cancer-related death, its incidence has decreased since 1960; the mortality rate from gastric cancer is declining more rapidly. Since the early 1960s, great effort has been directed at combatting this disease, and has led to a substantial increase in the overall 5-year survival rate, of up to 50 per cent. In contrast, there has been no improvement in gastric cancer treatment in Western countries. The prognosis for Western patients with gastric cancer is poor, with overall 5-year survival rates of only 20 per cent[2]. The reported reduction in the mortality rate from gastric cancer in western Europe and the USA is mainly due to its decreasing incidence over the past 50 years[1,3]. Thus, the prognosis of gastric cancer is much better for Japanese than for European or American patients[2,4–6].

This discrepancy in survival has been the subject of discussion for many years and may be attributed to earlier detection of the disease in Japan[5]. However, a difference persists, even in cases involving comparable pathological stages. Other possible explanations may be that the tumours exhibit different biological behaviour or that more radical gastric resection is practised in Japan[7–17]. It has been suggested by Western authors that differences in patient- and tumour-related factors are the main determinants of longer survival following surgical treatment in Japanese patients[58]. The D_2 and D_3 types of gastrectomy, including the removal of coeliac, juxtapyloric, retroperitoneal, peripancreatic and perisplenic (N_2, N_3) lymph nodes, as well as the perigastric (N_1) nodes[18–21], are used routinely in most operations for gastric cancer in Japan[22]. In the USA and UK, D_1 gastrectomy predominates, and only the perigastric (N_1) lymph nodes are removed in a gastric resection[5]. The resistance of Western surgeons to the use of more radical types of gastrectomy is attributed to uncertainty regarding the value of such procedures and the previous unfavourable results of such operations performed in the USA 20 years ago[23]. Thus, controversy exists with respect to the appropriate treatment of regional lymph node metastasis in gastric cancer. This review of the literature therefore considers the prognostic significance of regional lymph node metastasis and the therapeutic efficacy of lymph node dissection performed for gastric cancer.

Prognostic significance of regional lymph node metastasis

Prognostic factors in gastric cancer

Depth of tumour invasion and the presence of lymph node and distant (including peritoneal and hepatic disease) metastases are considered major prognostic factors in patients with gastric cancer[24–26]. Generally, depth of tumour invasion and lymph node metastasis have been recognized as significant prognostic factors in patients who undergo curable resection[27]. However, Msika *et al.*[25] and Huguier and co-workers[28] reported that only lymph node metastasis appeared as an independent factor in multivariate analysis in patients who underwent curative resection. Although many lymph nodes that contain metastases are enlarged, and the disease is apparent on gross examination, infrequently metastases are also found in small lymph nodes[29,30]. This makes it difficult to diagnose lymph node metastasis correctly during surgery. The inability to diagnose lymph node metastasis during operation and the high incidence of metastasis to the many lymph node groups of the stomach have prompted surgeons to perform extensive regional lymph node dissection[31,32]. The number of dissected nodes increased concomitantly with the proportion of patients with lymph node involvement[30]. If lymph node examination is insufficient, the nodal stage can be erroneously assessed as an earlier stage, whereby patient outcome becomes less favourable for that particular stage (stage migration phenomenon)[33–35]. An extended lymph node dissection and routine microscopic examination of all resected nodes can provide accurate information regarding lymph node status[34].

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Location of regional lymph node involvement

The regional lymph nodes of the stomach are classified into 16 areas and divided into four groups (N_1–N_4) according to tumour location[36]. Grossly, N_1 refers to perigastric nodes, N_2 nodes are located along the splenic and left gastric arteries and at the coeliac axis, N_3 nodes are located along the hepatoduodenal ligament and at the root of the mesentery, and N_4 represents the para-aortic and middle colic nodes. Maruyama *et al.*[24] reported 5-year survival rates in patients with metastases involving N_0, N_1, N_2, N_3 and N_4 levels of invasion of 82, 50, 24, 6 and 2 per cent respectively. Okusa *et al.*[37] gave 5-year survival rates of patients with metastases involving N_0, N_1 and N_2 levels of invasion of 81, 57 and 29 per cent respectively. Thus, significant differences between N_0 and N_1 ($P<0{\cdot}01$), and N_1 and N_2 ($P<0{\cdot}05$) groups have been demonstrated. Similarly, Haruyama[38] and Isozaki *et al.*[39] reported that the grouping of involved lymph nodes was significantly associated with survival (*Table 1*). However, this classification is too complicated to be used routinely, and more simple staging of lymph node involvement has been recommended[28,40].

Number of regional lymph nodes involved

Okusa and colleagues[37] reported that the 5-year survival rate decreased significantly as the number of metastases increased. The rate was 81 per cent for patients with no lymph node metastases, 63 per cent for those with one to three lymph nodes involved, 46 per cent for those with four to six nodes involved and only 29 per cent for those with more than six affected nodes. Significant survival differences were found between patients with zero and those with one to three involved nodes ($P<0{\cdot}01$), four to six *versus* seven or more nodes affected ($P<0{\cdot}05$), zero *versus* four to six involved nodes ($P<0{\cdot}01$) and one to three *versus* seven or more affected nodes ($P<0{\cdot}05$). Similarly, Haruyama[38] and Isozaki *et al.*[39] showed that the total number of involved lymph nodes was significantly associated with survival (*Table 1*). However, the greater the total number of positive nodes, the higher the incidence of involved nodes at multiple levels[37,38,41].

Opinions differ as to the relative importance of the total number *versus* the anatomical level of metastatic lymph nodes[38,39,42,43]. Isozaki *et al.*[39] reported that the long-term outcome was affected by the extent of lymph node involvement, but was not significantly affected by the number of nodes involved. However, Makino and coworkers[42] considered that the prognosis varies in patients with N_1 lymph node metastasis according to the number of involved nodes. Moreover, Haruyama[38] reported that, in patients with fewer than two metastatic lymph nodes, the 5-year survival rate did not differ between those with N_1 metastases and those with N_2 or N_3 metastases. Recently, Ichikura *et al.*[43] suggested that the number of lymph node metastases has a more adverse effect on the survival of patients with gastric cancer than the anatomical level of involved nodes. These findings may mean that regional lymph nodes are of biological rather than anatomical importance in terms of cancer treatment. Further study is necessary to evaluate whether the total number or anatomical level of metastatic nodes is more important in assessing the prognosis of patients with gastric cancer.

Efficacy of regional lymph node dissection

Extent of lymph node metastasis and lymph node dissection

In the early 1960s, Jinnai[18,19] recommended extended radical surgery to improve outcome in gastric cancer Subsequently, the concept of radical dissection of the lymph nodes has become an integral part of the surgical treatment of patients in Japan. Gastric resection is classified according to the extent of the accompanying nodal dissection[36]. D_0 represents gastric resection including incomplete dissection of the N_1 nodes; D_1 represents gastric resection including complete dissection of the N_1 nodes; D_2 is gastric resection including complete dissection of both N_1 and N_2 nodes; and D_3 is gastric resection including complete dissection of the N_1, N_2 and N_3 nodes.

Table 1 Five-year survival rate according to anatomical level and number of regional lymph node metastases

Level of involved nodes*	5-year survival rate (%)	*P*	No. of involved nodes	5-year survival rate (%)	*P*	
Okusa *et al* [37]						
N_0 (*n* = 238)	81	<0·01	0 (*n* = 238)	81		
N_1 (*n* = 123)	57	<0·05	1–3 (*n* = 85)	63	<0·01	<0·01
N_2 (*n* = 66)	29		4–6 (*n* = 42)	46	<0·05	0 05
N_3 (*n* = 6)	—		>6 (*n* = 68)	29		
Haruyama[38]						
N_0 (*n* = 295)	86	<0 001	0 (*n* = 295)	86		
N_1 (*n* = 157)	46		1–2 (*n* = 102)	54	<0·001	
N_2 (*n* = 143)	44		3–7 (*n* = 125)	49	<0·01	
N_3 (*n* = 18)	44		>7 (*n* = 91)	29		
Isozaki *et al.*[39]						
N_0 (*n* = 431)	86	<0·0001	0 (*n* = 431)	86	<0 0001	
N_1 (*n* = 182)	60	<0·0001	1–4 (*n* = 187)	60	<0·0005	
N_2 (*n* = 97)	33	<0·038	5–10 (*n* = 80)	36	<0·0002	
N_3 (*n* = 44)	17		>10 (*n* = 63)	12		
N_4 (*n* = 7)	0					

Values in parentheses are numbers of patients. *N_1, perigastric nodes; N_2, nodes located along the splenic and left gastric arteries and at the coeliac axis; N_3, nodes along the hepatoduodenal ligament and at the root of the mesentery; N_4, para-aortic and middle colic nodes

The basic principle of the operation is that the dissected area should always be wider than the actual lymphatic spread of the tumour[19]. Shiu *et al.*[44] have shown that inadequate lymphadenectomy relative to the nodal stage, as well as inadequate gastric resection, is markedly associated with shorter median survival and higher mortality rate. In this study the extent of lymphadenectomy, when analysed relative to the stage of nodal involvement (D minus N), revealed a significantly favourable effect afforded by wide lymphadenectomy; for N_0 tumours, the overall 5-year survival rate was 62 per cent when D minus N was 1·5 or higher, compared with 48 per cent when D minus N was less than 1·5. A similar effect was noted for N_1 tumours, but the number of patients studied was small. Moreover, in a multivariate study with the Cox model, inadequate lymphadenectomy relative to nodal stage was confirmed as an independent prognostic factor. However, it is possible that the Cox model could not exclude a bias in the distribution of the lymph nodes involved in this study, because the number of nodes with metastatic involvement was divided into only two groups: zero to three lymph nodes involved and four or more nodes affected.

In early gastric cancer the incidence of lymph node metastasis is only 1–5 per cent for tumours limited to the mucosa but approximately 20 per cent for those invading the submucosa. Of these 1–3 per cent of cases involved metastasis to the N_2 nodes[45,46]. Metastasis in the N_3 nodes occurs rarely[47]. Excellent outcome has been reported when subtotal gastrectomy is combined with either limited or extensive lymph node dissection[31,47]. Limited lymph node dissection may be indicated for some patients with early gastric cancer, particularly for malignancy restricted to the mucosa[47].

In more advanced gastric cancer, on the other hand, experience in Japan has shown that curative resection of the stomach combined with extended lymphadenectomy significantly improves the 5-year survival rate in patients with involved regional lymph nodes[7–12]. In contrast, Gilbertsen[48] reviewed 1983 patients with gastric cancer treated from 1936 to 1963, and found that between 1958 and 1963, when extended lymph node dissection was being performed, the survival rate decreased and operative mortality increased. Since Gilbertsen's review, extended lymphadenectomy has not been considered an integral part of gastric cancer treatment in Western centres. Moreover, a subsequent retrospective review[49] of European patients failed to demonstrate the importance of extended lymphadenectomy. Thus, controversy surrounds the therapeutic value of extensive gastric resection and regional lymph node dissection in the curative treatment of gastric cancer[48–51].

Retrospective and prospective non-randomized comparative studies

In a retrospective comparative study, Mine *et al.*[7] and Majima and colleagues[12] reported that, in patients with positive lymph nodes who underwent curative operation, the 5-year survival rate was considerably higher after D_3 resection than after D_2 resection (21 *versus* 10 per cent). However, this difference was not statistically significant. Inokuchi[8] and Kodama *et al.*[9] reported that, in similar patients, the 5-year survival rate was significantly higher after D_2 or D_3 resection compared with D_0 or D_1 resection (39 *versus* 18 per cent, $P<0{\cdot}0001$) (*Table 2*). In a prospective, non-randomized comparative study, on the other hand, Pacelli *et al.*[52] showed that the 5-year survival rate was significantly higher after D_2 or D_3 compared with D_1 resection (65 *versus* 50 per cent, $P=0{\cdot}01$). Moreover, in a multivariate study, the extent of lymphadenectomy appeared as an independent prognostic factor for survival ($P=0{\cdot}01$). Similarly, Siewert and co-workers[53] reported that the 5-year survival rate was significantly higher after D_2 resection than after D_1 resection (55 *versus* 27 per cent for stage II, $P<0{\cdot}001$; 38 *versus* 25 per cent for stage IIIA, $P=0{\cdot}03$) (*Table 3*). In a multivariate analysis, D_2 dissection was an independent prognostic factor of survival in patients with tumour stages II ($P<0{\cdot}001$) and IIIA ($P<0{\cdot}05$).

However, as Welch[23] has suggested, such a large increase in survival cannot be explained by the performance of more radical lymphadenectomy alone[50,52,54]. Retrospective Japanese studies have been performed on groups of patients from two different periods of time. Although caution must be exercised in drawing conclusions from these studies, they suggest that since 1960 the number of Japanese patients with N_2 or N_3 lymph node metastasis has decreased in association with an increase in the number with no node metastasis[10]. It has been suggested that the improved patient survival in Japan is due to an increased detection of early gastric cancer, attributed to the aggressive use of diagnostic tests such as air-contrast radiography, endoscopy, and endoscopy combined with multiple direct biopsies[31,50].

As mentioned above, the application of extended lymph node dissection induces substantial stage migration[33–35]. In a study by Siewert *et al.*[53], removal of 26 or more nodes

Table 2 Retrospective comparative studies of survival after regional lymph node dissection in patients with gastric cancer

Reference	Type of resection	No. of patients	No. with lymph node metastasis	5-year survival rate (%) Metastasis absent	Metastasis present	Overall
Inokuchi[8]	Simple resection (D_{0-1})	254	181 (71)	73	18	33
Kodama *et al.*[9]	Extensive lymph node dissection (D_{2-3})	454	245 (54)	81	39*	58*
Mine *et al.*[7] Majime *et al.*[12]	Conventional lymph node resection (D_2)	84	59 (70)	53	10	
	Extensive lymph node resection (D_3)	140	103 (74)	49	21	

Values in parentheses are percentages. D_0, incomplete dissection of N_1 lymph nodes; D_1, complete dissection of N_1 lymph nodes; D_2, complete dissection of both N_1 and N_2 lymph nodes; D_3, complete dissection of N_1, N_2 and N_3 lymph nodes. *$P<0{\cdot}0001$ (extensive node dissection *versus* simple resection) was defined as radical lymphadenectomy (D_2 resection), while extirpation of fewer than 26 nodes was considered standard lymphadenectomy (D_1 resection). In either retrospective or prospective non-randomized comparative studies, therefore, observed differences in survival result to a degree from differences in tumour staging or from the understaging of disease in patients who undergo the standard procedure[35]. Recently, Bunt *et al.*[35] reported that the application of systemic extended lymph node dissection in gastric cancer treatment induces substantial stage migration. The calculated effects of this stage migration on 5-year survival rate suggest an increase of 1 per cent in tumour node metastasis stage IA, 2 per cent in IB, 7 per cent in II, 15 per cent in 111A and 15 per cent in 111B.

Prospective randomized studies

Because of a lack of prospective randomized studies, the improved results of extended lymph node dissection have not been substantiated[51]. Critical review of the current Japanese literature does not lend overwhelming support to the stance that a prospective randomized trial would be unethical[51]. Such prospective randomized studies have been conducted in Western countries[55–58].

Dent *et al.*[55] reported that four patients in the D_1 group ($n = 22$) died from disease, as did five in the D_2 group ($n = 21$). There was no difference in survival at a median follow-up of 3·1 years. Robertson *et al.*[56] showed that overall survival after D_3 resection ($n = 30$) was significantly worse than after D_1 resection ($n = 25$) (median survival 922 *versus* 1511 days, $P < 0{\cdot}05$). However, they found no significant difference in survival between patients in the D_1 and D_3 groups when multivariate analysis was employed. Thus, two of these prospective randomized trials have failed to demonstrate the efficacy of extended lymph node dissection[55,56] (*Table 4*), although the number of patients in these studies was small[59].

In a recent study, Robertson *et al.*[56] documented an overall operative mortality rate of 2 per cent (one of 54 patients). In particular, the operative mortality rate in the D_3 total gastrectomy group was 3 per cent (one of 29), comparable with the present authors' previous results[30]. Despite a favourably low operative mortality rate in this series, the D_3 procedure was associated with considerable morbidity. However, another ongoing randomized clinical trial[57,58] involving a large series of patients, which should be completed in 1995, has shown that this extended technique can be performed without an increase in postoperative morbidity or mortality rates.

Comment

It remains controversial as to whether extended lymph node dissection is of therapeutic benefit or merely represents a staging procedure in patients with gastric cancer. In Japan, the mortality rate associated with gastric cancer remains high enough to justify all reasonable approaches towards achieving its reduction. Radiation therapy and chemotherapy are of only limited therapeutic value at present, whereas these modalities have demonstrated increasing efficacy in treating patients with breast cancer, permitting a reduced resection without jeopardizing tumour control. It is highly probable that the incidence of local recurrence is reduced by extended lymph node dissection[60]. Moreover, the operative mortality rate associated with extended surgery in Japan is less than 3 per cent[10,30], comparable with mortality rates for conventional resection in Western countries For these reasons, extended lymph node dissection appears to be the surgical procedure of choice for the curative

Table 3 Prospective comparative studies of survival after regional lymph node dissection in patients with gastric cancer

Reference	Type of resection	No. of patients	5-year survival rate (%)						
			Stage IA	Stage IB	Stage II	Stage IIIA	Stage IIIB	Stage IV	Overall
Pacelli *et al.*[52]	Limited lymph node dissection (D_1)	121	82		58	30		—	50
	Extensive lymph node dissection (D_{2-3})	117	86		66	49*		—	65†
Siewert *et al.*[53]	Standard lymph node dissection (D_1)	558	87	72	27	25	28	28	—
	Complete or radical lymphadenectomy (D_2)	1096	86	69	55‡	38§	18	16	—

D_1, complete dissection of N_1 lymph nodes; D_2, complete dissection of both N_1 and N_2 lymph nodes, D_3, complete dissection of N_1, N_2 and N_3 lymph nodes $^*P = 0{\cdot}02$, $^\dagger P = 0{\cdot}01$ (extensive *versus* limited node dissection); $^\ddagger P < 0{\cdot}001$, $^\S P = 0{\cdot}03$ (complete or radical lymphadenectomy *versus* standard dissection)

Table 4 Prospective randomized studies of survival after regional lymph node dissection in patients with gastric cancer

Reference	Type of resection	No. of patients	No of cancer-related deaths*	Mean survival (days)
Dent *et al.*[55]	Limited lymph node dissection (D_1)	22	4	—
	Extensive lymph node dissection (D_2)	21	5	—
Robertson *et al.*[56]	Limited lymph node dissection (D_1)	25	—	1511
	Extensive lymph node dissection (D_2)	29	—	922†

D_1, complete dissection of N_1 lymph nodes; D_2, complete dissection of both N_1 and N_2 lymph nodes *Median follow-up 3 1 years. $^\dagger P < 0{\cdot}05$ (extensive *versus* limited dissection) treatment of most patients with gastric cancer, at least until prospective randomized clinical trials involving a large series of patients have been successfully completed and the results reported[62].

On the other hand, the outlook for patients with gastric cancer has improved over the past 30 years. It seems likely that a combination of earlier diagnosis, better preoperative staging, more radical surgery and improved perioperative care has contributed to this improvement[61]. The value of systemic therapy in patients treated by extended lymph node dissection, compared with those with residual microscopic disease, should, therefore, be of interest. Moreover, it is essential that differences in the biological behaviour of gastric cancers in Japan and Western countries be investigated. Different dietary habits may influence not only the incidence of gastric cancer, but also its biological behaviour.

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Review

Renal ischaemia–reperfusion injury

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Ischaemia–reperfusion injury is a complex interrelated sequence of events that classically involves the vascular endothelium and activated leucocytes. During the ischaemic phase the endothelium is primed both to produce free radicals and to secrete chemoattractants. The resultant neutrophil sequestration serves to amplify the injury, but damage is not confined to the postischaemic area and more generalized effects typically follow. The situation in the kidney is complex for, while ischaemia primes the tissue for reperfusion damage, it also causes early and irreversible tubular injury. Furthermore, it appears that relatively less importance should be attached to the involvement of neutrophils than at other sites, and relatively more to a local postischaemic imbalance in the levels of nitric oxide and endothelin. Despite a greater understanding of the pathogenesis of ischaemia–reperfusion injury, effective treatment remains elusive and research is hampered by apparent species and organ-specific differences.

Renal ischaemia–reperfusion injury is not only an invariable consequence of transplantation but also results from circumstances such as aortic cross-clamping and resuscitation following systemic hypotension. This paper reviews the general pathophysiology of ischaemia–reperfusion injury, highlights the anomalous situation within the kidney and presents the current options available to ameliorate renal postischaemic damage.

Free radicals

A free radical is any species capable of independent existence that possesses one or more unpaired electrons and thus is chemically highly reactive. Foremost within biological systems are the reactive oxygen species, especially the superoxide (O_2^-) and hydroxyl ($OH^\cdot$) radicals. While molecular oxygen (O_2) is the most prevalent radical, its reactivity is limited by the particular configuration of the two unpaired electrons in its outer shell[1–7]. Apart from oxygen-centred radicals, several others are noteworthy: nitric oxide (NO)[8], both itself and after reaction[9] with O_2^- to generate $OH^\cdot$ via the intermediary peroxynitrite ($ONOO^-$), and the transitional metal-centred radicals such as perferryl radical (Fe^{3+}–O_2–Fe^{2+})[10]. The production of free radicals can be considered in three main contexts: exogenous, endogenous physiological, and endogenous pathophysiological.

Exogenous production

Electromagnetic radiation (ionizing radiation) and heat can induce the formation of intracellular radicals[11].

Endogenous physiological production

Mitochondria normally 'leak' some oxygen, which is reduced in the presence of reduced nicotinamide adenine dinucleotide (NADH)[12] to O_2^-. This low-grade production accounts in part for the prevalence of the O_2^- scavenger superoxide dismutase within both the cytosol[13] and mitochondria[3].

Endogenous pathophysiological production

Xanthine oxidase system. Depletion of adenosine 5'-triphosphate (ATP) during ischaemia[14] has two sequelae: (1) a rise in the concentration of hypoxanthine[15] (a breakdown product of ATP metabolism); and (2) the dysfunction of ATP-dependent membrane ion pumps with a consequent rise in both mitochondrial[16] and cytosolic[17] calcium levels. Normally, hypoxanthine is oxidized by the enzyme xanthine dehydrogenase to uric acid, although it can also be oxidized by xanthine oxidase, an isoform of xanthine dehydrogenase which transfers an electron to O_2 forming O_2^-[18]. Conversion of dehydrogenase to oxidase is under the influence of a calcium-dependent protease which is activated by ischaemia[19], tumour necrosis factor, interleukins 1 and 3, neutrophil elastase, the fifth component of the complement system (C5) and the chemotactic peptide *N*-formyl-Met-Leu-Phe[20,21]. The duration of ischaemia required for dehydrogenase to oxidase conversion varies from organ to organ, taking about 30 min in the kidney[6].

The Fenton reaction. Ferric iron is reduced to the ferrous state by O_2^- and is then able to donate an electron to hydrogen peroxide, which dismutes[5,11] to OH. The rate-limiting step[22] is the availability of hydrogen peroxide, as both xanthine oxidase and O_2^- are able to mobilize iron from the intracellular storage protein ferritin[23]. Angel *et al.*[24] have suggested that haemoglobin may act as a source of iron *in vivo*, although an increase in the level of free iron is seen in the postischaemic kidney even during reperfusion with an (oxygenated) asanguinous solution[14].

The plasma membrane. In addition to being a focus for free radical-induced cell injury, the plasma membrane can act as a site for the generation of reactive oxygen species. The postischaemic increase in intracellular calcium concentration is thought to activate phospholipase A_2, which initiates the arachidonic acid

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cascade[25]. Free radical generation[3] is linked to the consequent production of prostanoids[26–29].

Cellular targets for free radical injury

The highly reactive nature of free radicals dictates that their site of action must be close to their site of formation, and thus much interest has focused on free radical-mediated peroxidation of the lipid membrane. One assay for this is based on the reaction of malondialdehyde (one of the metabolites of lipid peroxidation) with thiobarbituric acid (the TBA test)[30], although doubts have been cast on the specificity of this test[31]. Utilizing the more specific high-performance liquid chromatography, McCoy *et al.*[32] found that there was little lipid peroxidation following ischaemia–reperfusion in the rat kidney. Other targets are structural and enzymatic proteins, which are denatured, and DNA, with consequent cross-linkage and scission[3,11].

Role of polymorphonuclear leucocytes

Like the endothelial cell[33], the polymorphonuclear leucocyte (PMN) is intrinsically capable of producing free radicals. However, while white cells play a significant role in ischaemia–reperfusion injury within certain organs, their role in extending renal injury is questionable.

Leucocyte attraction and activation

Initial chemoattraction is mediated by endothelial cells, and xanthine oxidase, whether in its own right or as a result of the secondary production of reactive oxygen species, has a chemoattractive effect[34], as has platelet activating factor (PAF)[35] which is released from endothelial cells in response to stimulation by reactive oxygen species. Activation and migration[36,37] are mediated via adhesion molecules on the endothelial cells and granulocytes (e.g. CD11/CD18). Adhesion, which is essential for the cytokine-induced respiratory burst[38], takes place in two phases. First, through the reversible, calcium-dependent rolling of PMNs on the endothelial selectin CD62[39], and then irreversibly via CD18, which is upregulated, probably via a protease enzyme released by the granulocyte[40]. Following adhesion, the system is augmented by cytokine production, particularly that of PAF, interleukins[41], tumour necrosis factor[42], and interferon γ[43]. These cytokines recruit and activate further PMNs[36], as well as upregulating adhesion molecule expression[44].

Leucocyte-mediated injury

An activated PMN can cause tissue destruction via three pathways.

Production of free radicals via the respiratory burst. The site of production of reactive oxygen species has been localized to a membrane-bound NADPH oxidase. The O_2^- generated reacts with hydrogen peroxide to form the relatively stable oxidant hypochlorous acid in a reaction catalysed by myeloperoxidase released from PMN granules[45]. Marletta *et al.*[46] have demonstrated that activated PMNs are also capable of producing nitric oxide, although this may in fact be impaired in ischaemia–reperfusion injury[47].

Release of intrinsic enzymes. Of the 20 or more enzymes present within the PMN granules, elastase is especially destructive. The effect is exaggerated because hypochlorous acid denatures the natural antielastases α_1-antitrypsin, α_2-macroglobulin and secretory leucoproteinase inhibitor[45].

Physical obstruction of capillaries. Capillaries may become physically blocked by PMNs[48], with inevitable impairment of the microcirculation and extension of the ischaemic insult. This 'no-reflow' phenomenon may be due to an activation-dependent increase in PMN stiffness rather than to adhesion *per se*[37], as the use of a monoclonal antibody to block the CD11/CD18 complex does not prevent plugging[49].

Polymorphonuclear leucocytes and renal ischaemia–reperfusion injury

The use of a monoclonal antibody to the CD11/CD18 complex prevents both adhesion and migration[50]. While such an antibody is effective in ameliorating both skeletal and cardiac muscle ischaemia–reperfusion injury[51,52] it affords no protection against renal injury[53]. Similar results have been demonstrated using leucocyte-depleted blood. Although Klausner *et al.*[54] showed a significant benefit for the postischaemic kidney, others have found no protective effect, either functionally[55] or morphologically[53]. Conversely, Pearl *et al.*[56,57] demonstrated that leucocyte depletion during cardiac transplantation decreased both biochemical dysfunction and histological damage, although without any apparent functional benefit.

Postischaemic endothelium

The endothelium produces both endothelin and nitric oxide, which are important in cardiovascular and renal microvascular homoeostasis[58,59]. Within the arterial circulation nitric oxide tends to reverse the vasoconstrictive effects of endothelin, whereas the opposite is the case in veins[60], with vasoconstriction predominating. In ischaemia–reperfusion injury the physiological ratio of endothelin : nitric oxide is altered and this may be pivotal to the resultant injury.

Endothelin and nitric oxide

Endothelin, a 21-residue peptide, is the most potent vasoconstrictor yet identified[61], and the kidney is approximately ten times more sensitive than other vascular beds[62]. During ischaemia, endothelial transcription of endothelin is amplified[63], leading both to an upregulation of CD11/CD18 expression[64] and to the activation of the alternative pathway of the complement system[65].

Nitric oxide[66] is an important factor in the maintenance of normal diuresis, natriuresis and glomerular filtration rate (GFR)[67]. It is synthesized from L-arginine by the enzyme nitric oxide synthase (NOS), which exists in four isoforms[68–74]. NOS I and III are constitutive enzymes (cNOS) that are calcium and calmodulin dependent, while NOS II and IV are inducible (iNOS), i.e. their expression depends on transcription and, once induced, activation is prolonged[75]. In the kidney, NOS I is predominantly expressed in the macula densa[67] where the nitric oxide produced is thought to act in a paracrine fashion to control both arteriolar vascular tone and local renin release[71,76]. NOS III is expressed within the arteriolar endothelium, while NOS II has been localized principally to the preglomerular portion of the afferent arteriole and to the mesangial cells[73].

The endothelium in postischaemic tissues generally becomes refractory to the vasodilatory action of nitric oxide[47,77], an effect that may last for more than 12 weeks[78]. In the kidney, not only is the action of nitric oxide impaired[79,80] but there is also increased production of endothelin[81] with a consequent decrease in both renal blood flow and GFR[82,83], possibly mediated by PAF[84] produced locally in the glomerulus[85]. In an *ex vivo* model, PAF has been shown to be vasodilatory at low concentrations, probably by upregulating cNOS[75,86], while at higher concentrations vasoconstriction predominates[87].

Idiosyncrasies of renal ischaemia–reperfusion injury

Several factors account for the particular features of renal ischaemia–reperfusion injury. Morphological studies have demonstrated that ischaemia irreversibly damages the distal segment of the proximal tubule (S3), while the more proximal segments suffer reversible injury. S3 cells undergo necrosis and are shed into the tubule lumen[88]; this is thought to exacerbate the decrease in GFR. Mason *et al.*[89,90] have demonstrated that renal ischaemia leads to erythrocyte sludging in the outer medullary inner stripe capillaries. This is not improved by aspirin or heparin treatment, although a reduction of the haematocrit to about 30 per cent is effective in improving both renal perfusion and postischaemic function.

During the 'maintenance phase' of postischaemic renal failure (up to 10 days from the primary injury) secondary damage is brought about by Tamm–Horsfall protein. This is a mucoprotein produced by the thick ascending limb of the loop of Henle; it is soluble at the low sodium concentration normal in this part of the nephron. However, after ischaemic damage there is impaired reabsorption, the intraluminal sodium concentration rises and the Tamm–Horsfall protein gelatinizes. The recovery of affected nephrons is dependent on washing this gel out, a process not aided by the increased renal vascular resistance and decreased glomerular capillary pressure seen in response to the obstruction[91].

Camazine *et al.*[92] have shown that a proportion of the mesangial glomerular cells express Fc and C3 receptors, are highly phagocytic and so are presumably capable of generating reactive oxygen species. The presence of this intrinsic cell population may account in part for the ambivalent role of PMNs in renal ischaemia–reperfusion injury[51,55,93]. A further problem is that animal models have displayed clear differences between species. Southard *et al.*[94] showed that human and canine kidneys have a xanthine oxidase : superoxide dismutase ratio 40 times greater than that seen in the rat, and so may be less susceptible to damage by reactive oxygen species. Other disparities are also evident when comparing postischaemic renal blood flow[95] and the lack of correlation between morphological changes and renal function[96].

Renal transplantation

In many situations of ischaemic damage the clinician has little control of the situation. However, one area where ischaemia is amenable to intervention is solid organ transplantation.

The traditional source of kidneys for transplantation, from cadaveric donors via the intensive care unit, is declining[97]. A further source of grafts is from asystolic or non-heart-beating donors[98]; kidneys are harvested when cardiopulmonary resuscitation has been unsuccessful. Such grafts are exposed to significant warm ischaemia and so have a higher incidence of delayed primary function, acute tubular necrosis[99] and primary non-function than cadaveric grafts exposed to predominantly cold ischaemia. Renal preservation before transplantation can be achieved in one of two ways, either on a continuous perfusion machine or by storage in ice. Simple cooling allows preservation for 12 h[100] by slowing down cellular reactions[101], and this can be extended to 72 h by flushing the kidney with University of Wisconsin solution[102] before storage in ice. University of Wisconsin solution contains glutathione and adenosine to aid the regeneration of ATP; lactobionate, phosphate and raffinose to prevent cellular swelling; and several other components[103] including allopurinol.

Renal ischaemia

In a canine model Satoh *et al.*[104] have demonstrated that 30 min of warm ischaemia followed by cold storage preservation leads to an endothelium-dependent rise in renal vascular resistance that is almost certainly a result of impaired secretion of nitric oxide. Less than 1 h of warm ischaemia of the human kidney is not usually associated with more than temporary dysfunction[100], while 3 h or more results in irreversible damage[9]. Within these bounds lies a therapeutic window; a similar opportunity exists during cold ischaemia preservation of 18–48 h, when treatment with superoxide dismutase or allopurinol is efficacious[105–107]. Outside such therapeutic windows renal damage results from ischaemia *per se*, as free radical production actually diminishes with prolonged ischaemia[108].

Renal ischaemia and graft rejection

The duration of ischaemia not only affects initial graft function: several studies have linked prolonged cold ischaemia to the development of chronic vascular rejection. The somatostatin analogue angiopeptin has been shown to prevent or delay chronic vascular rejection and is currently being evaluated[109].

Renal transplantation results in a marked local cytokine response and interferon γ is particularly prominent. This response leads to an increased expression of major histocompatibility complex (MHC) class II molecules[43] which, by day 5, are strongly expressed on all the tubular epithelial cells as well as the non-glomerular endothelium[110]. MHC molecules play an important role in the alloresponse, and Loutfi *et al.*[111] have demonstrated that their upregulation is indicative of graft rejection. Attempts to prolong graft survival by downregulating MHC II expression with monoclonal antibodies[112] and, particularly, by PUVA pretreatment (i.e. the injection of 8-methoxypsoralen before harvest followed by ultraviolet A irradiation of the graft during hypothermic preservation)[113] have shown some promise. Interestingly, monoclonal antibodies to MHC II molecules lead to the upregulation of iNOS, at least in macrophages, where they may mimic cell–cell interaction with T lymphocytes[114]. This iNOS upregulation may account for the increase seen in plasma nitrate levels (a stable end-product of spontaneous nitric oxide conversion in blood) following renal and liver transplantation. The levels of nitric oxide peak around day 5 after transplantation, and also increase significantly during rejection[115].

Therapeutic indications and interventions

Ischaemic phase

Two areas lend themselves to intervention: first, the conversion of xanthine dehydrogenase to xanthine oxidase and, second, the reduction of high-energy phosphate compounds[116].

Calcium influx and dehydrogenase to oxidase conversion. Several studies have demonstrated the role of calcium channel blockers in improving primary graft function following renal transplantation[117,118], and Green *et al.*[14] have suggested that this is due to the prevention of calcium influx during the ischaemic phase. The fact that dehydrogenase to oxidase conversion is calcium dependent[6] may be one reason that calcium channel blockers prevent injury, although calcium influx into the cytosol also activates phospholipases which potentiate membrane damage, arachidonic acid metabolism and mitochondrial injury[119]. Other possible modes of action for calcium channel blockers exist. By decreasing calcium influx into erythrocytes during ischaemia, red blood cell deformability is maintained, which aids microvascular perfusion[120]. More importantly perhaps, endothelin-induced vasoconstriction is reliant on calcium influx and this has been shown to be antagonized by nicardipine[59]. Dehydrogenase to oxidase conversion is also protease dependent, and the use of the protease inhibitor aprotinin to block this conversion has reportedly led to a significant improvement in the degree of postischaemic muscle oedema and, by implication, to a decrease in microvascular damage[121].

Regeneration of adenosine 5'-triphosphate. Although ATP levels fall quickly during ischaemia, tissue viability is not affected in such a dramatic manner; it appears that the ability to resynthesize ATP after ischaemia is more important than the temporary reduction in ATP levels[122]. *In vitro* studies using rabbit renal proximal tubules have demonstrated that the administration of extracellular ATP–magnesium chloride ($MgCl_2$) significantly improves cellular respiratory function during recovery from anoxia[123]. It also restores membrane permeability towards normal[124], a fact confirmed in the kidney by Mandel *et al.*[15], who also found complete recovery of cellular ATP levels with the extracellular administration of ATP–$MgCl_2$, adenosine diphosphate–$MgCl_2$ or adenosine monophosphate–$MgCl_2$. Although *in vitro* studies[15] suggest that regeneration of intracellular ATP is dependent on extracellular adenosine, the addition of adenosine–$MgCl_2$ to the postischaemic rat kidney has produced little benefit in terms of renal function[125]. One reason for this discrepancy may be that extracellular adenosine exerts a negative influence on *in vivo* renal function by causing afferent arteriolar constriction[126].

Reperfusion phase

Manipulation of free radical production. Both superoxide dismutase, a scavenger of reactive oxygen species, and allopurinol, a xanthine oxidase inhibitor[127], have a protective effect in most models of renal ischaemia[128–131]. However, Gamelin and Zager[132] failed to demonstrate any such benefit and question whether reactive oxygen species are consistent mediators in postischaemic renal failure. Catalase, a hydrogen peroxide scavenger, affords no protection for the postischaemic kidney, possibly because its large size limits glomerular filtration and thus availability[131]. Alternatively, it may be because, unlike superoxide dismutase, catalase does not scavenge O_2^- and so does not prevent the breakdown of nitric oxide[133] and initiation of the Fenton reaction[134]. Further along the pathway the use of the iron chelators desferrioxamine and deferoxamine to minimize the production of OH via the Fenton reaction has shown some success both *in vitro* and *in vivo*[8,31]. Menasché *et al.*[135,136] have demonstrated that deferoxamine limits the production of reactive oxygen species and lipid peroxidation associated with human cardiopulmonary bypass. In a series of experiments in rabbits, Green *et al.*[14,137,138] have shown that desferrioxamine affords some protection to reperfused kidneys after exposure to both cold and warm ischaemia. In an endeavour to avoid the toxicity and short half-life of these chelators, others have been sought by binding deferoxamine to biocompatible polymers[139]. However, dextran-conjugated deferoxamine does not undergo renal filtration and in a rat model provided no protection[140].

Membrane stabilizers. Pavlock *et al.*[141] demonstrated that 2 h of warm ischaemia followed by reperfusion of the rabbit kidney leads to severe mitochondrial damage that can be completely prevented by pretreatment with chlorpromazine; this is not so after 3 h of warm ischaemia. A recently described group of compounds, the 21-aminosteroids or lazaroids, have been shown to inhibit both iron-catalysed lipid peroxidation and arachidonic acid metabolism[11,142]. Although no data exist for their efficacy in reducing renal ischaemia–reperfusion injury, they preserve myocyte viability in a skeletal muscle model[143].

Manipulation of arachidonic acid metabolism. Inhibition early in the pathway using the cyclo-oxygenase inhibitor ibuprofen prevents the rise in thromboxane levels normally seen in postischaemic kidneys, but also inhibits a beneficial increase in prostacyclin (PGI_2)[27]. The use of a specific thromboxane synthetase inhibitor circumvents this and has been shown to decrease histological damage in renal ischaemia–reperfusion injury[144]. Alternatively, thromboxane receptors may be blocked and this has the additional benefit of preventing the action of a vasoconstrictive prostaglandin (8-epi-prostaglandin $F_{2\alpha}$, produced through a non-cyclo-oxygenase pathway) via thromboxane A_2 receptors[145,146]. Another way to increase the prostaglandin : thromboxane ratio is to administer the stable semisynthetic prostacyclin analogue Iloprost (Schering Healthcare, West Sussex, UK). Neumayer *et al.*[147] showed that a 7-day intra-aortic infusion of Iloprost following canine renal ischaemia–reperfusion injury improved both the GFR and early renal blood flow. Furthermore, the addition of Iloprost to the perfusate of cadaveric renal grafts results in improved early function and a decreased incidence of primary non-function[123] Using a different PGI_2 analogue, Suzuki *et al.*[148] have shown that pretreatment before rodent hepatic ischaemia results in improved cell survival as measured both morphologically and biochemically. Associated with the protective effect afforded by mannitol in renal ischaemia–reperfusion injury[138,141] is a concomitant decrease in thromboxane A_2 production[149]; however, this is probably secondary to its role as a free radical scavenger rather than to any direct effect on thromboxane A_2 production.

Other treatment strategies. The infusion of a PAF antagonist before inducing ischaemia has a protective effect in both renal and gut models[150,151]. As PAF is thought to mediate the effects of endothelin within the ischaemic kidney, it is not surprising that use of an antiendothelin antibody also improves postischaemic renal function[84,152]. Mandel *et al.*[153] have used extracellular glutathione, a scavenger of reactive oxygen species, to protect renal proximal tubules from anoxia *in vitro*, with an improvement in function during reoxygenation. This cytoprotective effect appears to be related to the intracellular production of glycine from glutathione, rather than to glutathione itself. Exogenous thyroid hormone has been shown to protect kidneys subjected to ischaemia–reperfusion injury[119], possibly via stimulating mitochondrial respiration. Atrial natriuretic factor (ANF) is a polypeptide hormone, stored within atrial granules and also at non-cardiac sites (most notably the kidney), which functionally is natriuretic, hypotensive and inhibits renin and aldosterone secretion[154]. Shaw *et al.*[155] have demonstrated functional and morphological protection in renal ischaemia–reperfusion injury following ANF administration after the ischaemic period. ANF appears to increase the GFR by producing efferent vasoconstriction, thereby increasing glomerular capillary pressure[156], but the marked systemic hypotensive effect of ANF has precluded clinical trials. Conger *et al.*[157,158] circumvented this by infusing dopamine with the ANF; this maintained the GFR at control levels while preventing hypotension.

Conclusion

Ischaemia–reperfusion injury involves a complex inter-related sequence of events[159]. In the majority of organs ischaemia primes the tissue for the injury incurred during reperfusion, the injury being principally mediated by free radicals and PMNs. In the kidney, however, the situation is somewhat more complex as ischaemia itself causes early irreversible damage. Furthermore, while the involvement of free radicals early in renal reperfusion injury and the importance of the altered nitric oxide : endothelin ratio are of undoubted significance, the role of PMNs remains unclear.

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Value of routine intraoperative cholangiography in detecting aberrant bile ducts and bile duct injuries during laparoscopic cholecystectomy

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A prospective study was performed to determine the frequency and type of bile duct abnormalities, and to determine whether routine use of intraoperative cholangiography during laparoscopic cholecystectomy might aid in the prevention of bile duct injuries. Overall, anatomical aberrations of the bile ducts were found in 98 (19 per cent) of 513 cholangiograms. The most common anomalies were at the hepatic confluence and constituted different types of right hepatic subsegmental ducts draining separately into the biliary tree ($n = 43$, 8·4 per cent), either close to the cystic duct or directly into the cystic duct. Three bile duct injuries (0·5 per cent) occurred during the study period. These results show that routine intraoperative cholangiography is feasible and provides valuable information about the anatomy of the biliary tract, thereby improving the safety of laparoscopic cholecystectomy. If an injury to the biliary tract occurs early during operation, the cholangiogram allows the surgeon to detect the injury, to make a prompt repair and thereby reduce the morbidity associated with a delayed diagnosis. Routine use of intraoperative cholangiography is strongly recommended.

Intraoperative cholangiography has generated considerable interest and controversy since its inception in 1932. Mirizzi[1] was the first to recommend use of routine intraoperative cholangiography based on the prevalent occurrence of unsuspected bile duct pathology. The introduction of laparoscopic cholecystectomy, in which additional technical skill is required to perform a cholangiogram, has refocused the debate. The advocates of routine intraoperative cholangiography stress its value in delineating the biliary anatomy, thereby preventing bile duct injuries[2–4], while others point out that many ductal injuries occur in spite of cholangiography or before the procedure is undertaken, and therefore conclude that it should be performed selectively[5–7]. With the added potential hazards of traction of the gallbladder and the use of diathermy or laser dissection, the risk of causing bile duct injury may be greater during laparoscopic than open cholecystectomy. Injuries to the common bile duct (CBD) have been reported in up to 0·5 per cent (usually 0·2–0·3 per cent) of patients undergoing open cholecystectomy[8,9]. In the initial reports on laparoscopic cholecystectomy, the incidence of major bile duct injuries was approximately 1 per cent[10,11]. In a recently published clinical review comprising 21 series from Europe and the USA, the overall incidence of laparoscopic bile duct injury was 0·6 (range 0·1–2·9) per cent[12].

The purpose of this study was to determine the frequency and type of bile duct aberrations, and to examine the feasibility and preventive value of routine intraoperative cholangiography during laparoscopic cholecystectomy.

Patients and methods

Between January 1991 and May 1994, 630 patients who presented for elective or acute laparoscopic cholecystectomy were studied prospectively. There were 199 men (32 per cent) and 431 women (68 per cent) with median age 53 (range 11–86) years. Intraoperative cholangiography was attempted in 603 patients (96 per cent) and failed in 13 (2 per cent), resulting in an overall performance rate of 94 per cent (590 of 630). A common reason for failure was the inability to cannulate the cystic duct. No attempts were made to do cholangiography by direct puncture of the gallbladder or CBD.

Preoperative investigations included hepatobiliary ultrasonography and liver function tests. Clinical (jaundice, cholangitis or pancreatitis) or laboratory findings indicating the presence of bile duct stones were recorded. Patients with such signs underwent endoscopic retrograde cholangiography (ERC) before operation, and endoscopic duct clearance was attempted when stones were apparent. The authors perform laparoscopic cholecystectomy with the four-trocar technique[13] and the use of electrocautery. Dissection of the cystic duct starts with the gallbladder and a metallic clip is applied to the cystic duct close to the infundibulum of the gallbladder. No attempt is made to identify the cystic/hepatic duct junction. The cystic duct is partially opened with scissors, and a 4-Fr ureteric catheter (Rüsch AG, Kernen, Germany) is introduced percutaneously (through a syringe) into the cystic duct where it is secured by a loosely closed clip. The patient is placed in the Trendelenburg position to allow filling of the hepatic radicals. In all patients a mobile C-arm unit with high-resolution digitized fluoroscopic imaging (Exposcop CB 7-D; Ziehm, Nürnberg, Germany) was used. During injection of contrast medium the filling and delineation of the biliary tree are followed on the image intensifier. The technique allows adjustment of the C-arm position to get different projections in order to minimize the incidence of false-positive and false-negative cholangiograms.

At operation, the cholangiogram was primarily evaluated by the operating surgeon who, when necessary, was able to communicate the fluoroscopic image to a radiologist. Of the total of 590 cholangiograms, 513 (87 per cent) were stored and reviewed in detail by one radiologist.

Telephone assessment of subjective well-being or clinical examination at the outpatient department was carried out for 608 (96 per cent) of the 630 patients within 4–8 weeks after discharge from hospital. It was also aimed to perform a follow-up examination and analysis of liver function tests 6 months after the operation, but for various reasons, including advanced age, it was possible to carry out that examination in only 459 patients (73 per cent).

Results

Aberrant bile ducts

Seventy-seven cholangiograms were excluded from evaluation of the occurrence of aberrant bile ducts

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because the fluoroscopic images were not stored. Of the remaining 513 cholangiograms, 98 (19 per cent) (*Fig. 1*) showed anatomic variations, and at least 62 (12 per cent) of these were of surgical relevance (*Fig. 1a–f*).

Ductal aberrations were most common at the hepatic confluence and constituted different types of right hepatic subsegmental ducts ($n = 43$, 8·4 per cent) draining separately into the biliary tree (*Fig. 1a, b* and *d*). The inlets of these aberrant ducts were either very close to ($n = 28$) (*Figs 2* and *3*) or on the cystic duct ($n = 15$) (*Fig. 4*). In one case the cystic duct drained into the right hepatic duct (0·2 per cent), and in 16 cases (3·1 per cent) the cystic duct entered the common hepatic duct close to the confluence of the main right and left hepatic ducts. In a further two patients (0·4 per cent) there was a very low confluence with a short common duct (2–3 cm) (*Fig. 1c*). In another variation for cystic duct entry the duct connects with the left side of the CBD, passing either in front of or behind the duct. This occurred in 36 patients (7·0 per cent) (*Fig. 1g*).

There were no complications caused by the cholangiographic procedure.

Bile duct injuries

There were three (0·5 per cent) registered bile duct injuries. They occurred at cholecystectomy numbers 74, 127 and 380.

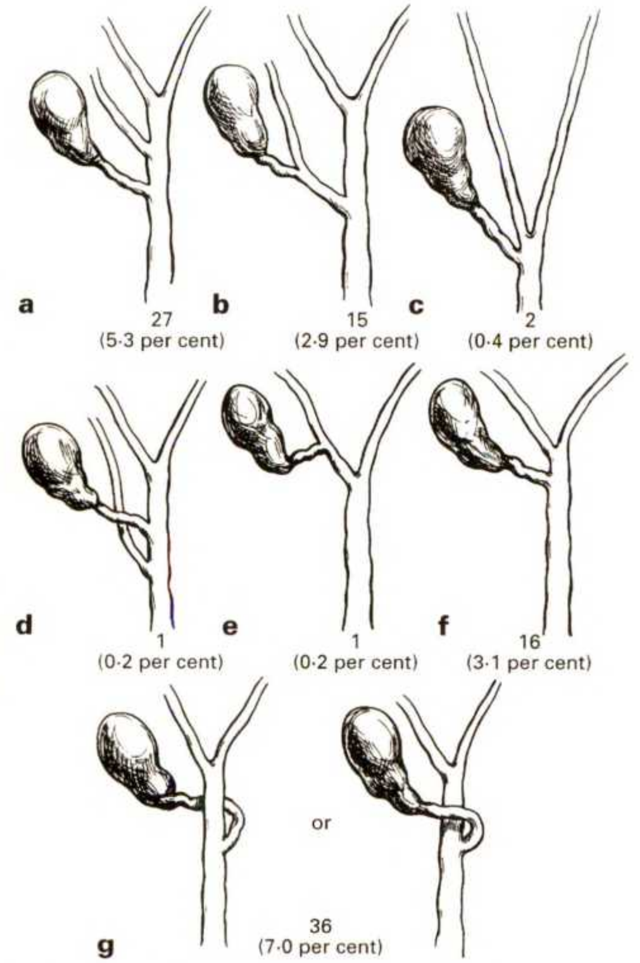

Fig. 1 Frequency of anatomical variations of bile ducts in 513 patients undergoing intraoperative cholangiography during laparoscopic cholecystectomy

Patient 1. A 61-year-old woman underwent laparoscopic cholecystectomy because of an ongoing attack of acute cholecystitis. Intraoperative cholangiography identified the cholangiography catheter placed in the distal part of the CBD and a clip occluding the proximal CBD. The diameter of the CBD was 4 mm. The operation was converted to an open procedure, the small ductotomy was repaired, and a T tube was inserted. A second intraoperative cholangiogram showed the cystic duct entering a slender aberrant right hepatic duct. Cholecystectomy was performed and, when a normal cholangiogram was seen 6 days later the T tube was removed. The patient suffered from pericarditis after operation, but recovered and was discharged 12 days after surgery. After 32 months of follow-up there are no signs of biliary stricture.

Patient 2. A 65-year-old man had laparoscopic cholecystectomy performed as an elective procedure, but 2 months earlier the patient had been treated conservatively for acute cholecystitis. Endoscopic sphincterotomy had been performed for CBD stones before operation. ERC showed normal anatomy of the bile ducts. The operation was converted early because of severe inflammation and adhesions. At the open procedure, a slender (less than 5 mm) CBD was mistaken for the cystic duct and was partially transected at the junction of the cystic and common ducts. The injury was recognized at intraoperative cholangiography and repair was undertaken by closing the defect and inserting a T tube, which was removed after 1 week. There have been

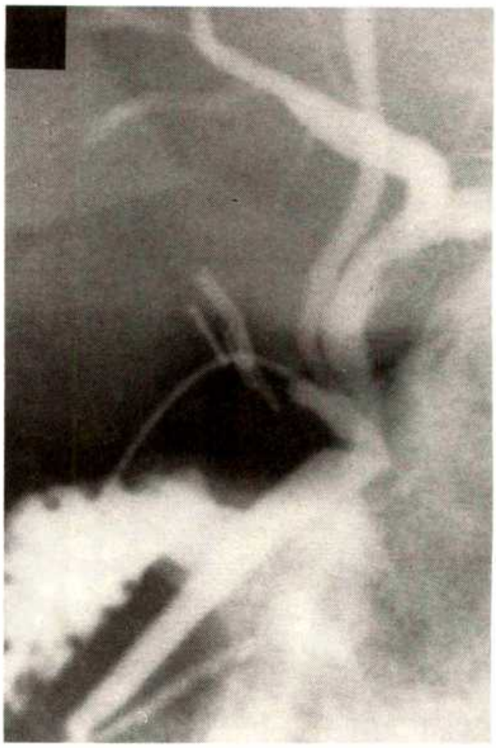

Fig. 2 An aberrant right hepatic duct entering the common hepatic duct near the junction of the cystic and common bile duct

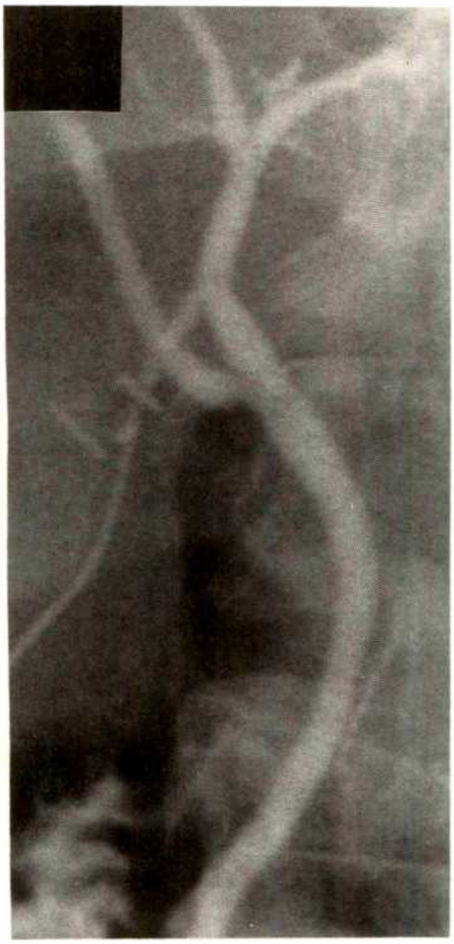

Fig. 3 Insertion of the cystic duct between the right hepatic duct and an aberrant hepatic duct joining the common bile duct

no signs of biliary stricture during a follow-up period of 28 months.

Patient 3. A 29-year-old woman underwent elective laparoscopic cholecystectomy. The operation was converted to an open procedure because of bleeding and unsatisfactory demonstration of the proximal bile ducts on cholangiography. The CBD, which was 3–4 mm in diameter, was accidentally opened. It was closed over a T tube, and secondary cholangiography showed cystic duct leakage which subsided spontaneously within 2 weeks. However, stricture of the common hepatic duct was recognized and the T tube was left in place for 6 months. After removal of the T tube, the common hepatic duct stricture was dilated endoscopically on seven occasions over 14 months. Between the dilatations, an endoprosthesis with gradually increasing diameter (7 to 11 Fr) was left in place. Stones developed above the stricture but could be removed endoscopically on two occasions. Seven months after the last dilatation and removal of the endoprosthesis, the patient is free from symptoms.

Bile duct leakage

Bile duct leakage after operation occurred in four patients (0·6 per cent). Two had laparoscopic cholecystectomy for acute cholecystitis and two were elective cases. One had leakage from a small duct in the gallbladder bed and three had cystic duct leakage. Three patients were successfully treated with biliary stenting, which in one patient was combined with percutaneous catheter drainage. The endoprostheses were removed after 4 weeks. In one patient stenting was not possible because of a B-II gastric resection. This patient was managed surgically with insertion of a T tube. All four patients are well after a median follow-up of 21 (range 18–26) months.

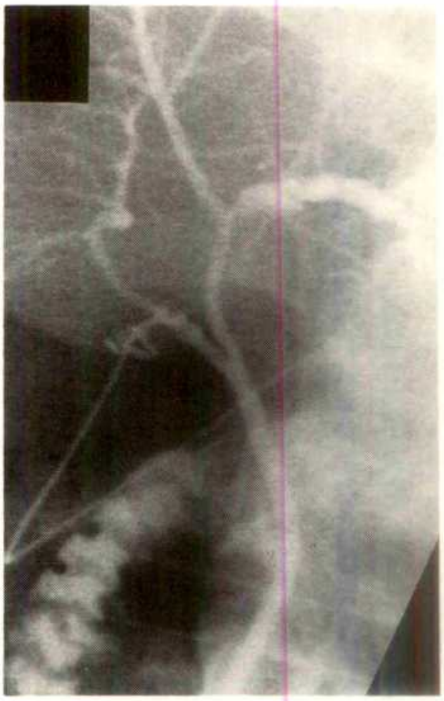

Fig. 4 Cystic duct entering an aberrant right hepatic duct

Discussion

The incidence of aberrant bile ducts is between 14 and 28 per cent in autopsy series[14,15]. Moossa *et al.*[16,17] emphasized that the presence of a bile duct aberration does not excuse bile duct injury, and that intraoperative diagnosis of anatomical variations of the biliary tract contributes greatly to the safety of laparoscopic cholecystectomy. To discover anatomical variations and bile duct stones, some institutions perform intravenous cholangiography (IVC) before operation. However, the resolution of IVC is limited, and there is a low diagnostic sensitivity. Goodman *et al.*[18] reported that only 55 per cent of IVCs were adequate and that the diagnostic error rate was 40 per cent, largely caused by false-negative findings. In a recently published series[19], IVC was diagnostic in 4 (27 per cent) of 15 patients with aberrant ducts, whereas direct endoscopic or intraoperative cholangiography was always diagnostic. Since the introduction of laparoscopic cholecystectomy, the trend has been for surgeons to abstain from intraoperative cholangiography, probably because of initial technical difficulties in performing the procedure[12]. However, it is reasonable that the same criteria for cholangiography be applied to laparoscopic as to open cholecystectomy. Several techniques described for performing intraoperative cholangiography during laparoscopic cholecystectomy have success rates of around 90 per cent[2,3,20,21].

There is no doubt that information on the presence of ductal aberrations is important for the surgeon. At laparoscopic cholecystectomy, the most critical manipulation with regard to the occurrence of anatomical variations is dissection of the cystic duct and artery in Moosman's area (a circular area 30 mm in diameter in the cystohepatic duct angle, bordered medially by the common hepatic duct and inferiolaterally by the cystic duct)[22]. In a series of 250 cadaver dissections 85 per cent of aberrant ducts were found within this zone[23].

The aberrant bile duct is usually a branch emerging from the right lobe of the liver (*Figs 1a, b* and *d*). The dorsocaudal region gives rise to these aberrant ducts more frequently than the ventral cephalic region[24]. Several studies have shown the lack of interductal communication within the liver, which means that the aberrant duct may be the only drainage from that particular part of the liver[15]. When such an aberrant duct enters the main duct near the cystic duct or receives the cystic duct, an injury can easily occur that results in partial or total segmental duct occlusion. As shown in this study, the prevalence of such ducts is relatively high (8·4 per cent), and they should be looked for at intraoperative cholangiography. The cystic duct varies in length as well as in the level and pattern of conjunction with the common duct (*Figs 1c, f* and *g*). It has been reported that up to 26 per cent of cystic ducts enter either above or below the expected site in the mid-portion of the common duct, and the literature indicates that the course of the two ducts is parallel in up to 20 per cent of cases[15]. Drainage of the cystic duct into the main right hepatic duct is uncommon (*Fig. 1e*), but when it occurs there is a great risk of ligation or transection of the right duct.

Iatrogenic bile duct injury often has a poor outcome, which can be avoided if the injury is recognized and repaired immediately[17,25]. Regional medical centres have reported a dramatic increase in the number of referrals for management of bile duct injuries following laparoscopic cholecystectomy[16,26–28], but as many of these injuries are not recorded in reports on laparoscopic cholecystectomy, it is difficult to know their true incidence.

The pattern of bile duct injuries associated with laparoscopic cholecystectomy is almost identical to that in open cholecystectomy, i.e. the duct is damaged at the level of or above the entrance of the cystic duct, presumably during dissection within Moosman's area[24,25]. The most severe injury occurs when application of clips, excessive use of electrocautery, or laser energy traumatizes the right and/or common hepatic duct, resulting in a biliary stricture. The most common type of bile duct injury occurs when the surgeon mistakes the common duct for the cystic duct, transects or ligates it, and excises the extrahepatic biliary tree along with the gallbladder[16,26,27]. This may be avoided if the principle is followed of never transecting a duct until it has been identified. Then only a choledochotomy for cholangiography will have been done, as illustrated by patients 1 and 2 in the present series. The greater traction on the gallbladder required during laparoscopic cholecystectomy may distort the anatomy so that the CBD may be mistaken for the cystic duct. The cholangiogram serves as a 'road map' and helps prevent transection of the CBD or an aberrant segmental hepatic duct.

It is obvious from the literature that over 90 per cent of patients referred to experienced medical centres because of bile duct injuries after laparoscopic cholecystectomy did not undergo cholangiography at the primary operation, resulting in delayed diagnosis in the majority of patients. The advantage of repairing ductal injuries immediately is undisputed. If patients are readmitted with cholangitis and/or jaundice, about 25–50 per cent suffer complications after reoperation. Furthermore, the overall immediate postoperative mortality rate caused by benign bile duct strictures is 10–20 per cent, and the long-term mortality rate is approximately 30 per cent. High bile duct strictures (Bismuth grade II–IV) have the worst prognosis, especially if a previous attempt at reconstruction has failed[17,26,28–30].

Although intraoperative cholangiography cannot compensate for failing to perform a meticulous dissection, routine intraoperative cholangiography decreases the incidence and severity of bile duct injuries[31]. In a recent study, Cuschieri *et al.*[3] showed that 4·8 per cent (23 of 483) of cholangiograms yielded important information that influenced the course of action taken by the surgeon, and that four patients (0·8 per cent) would undoubtedly have been at a disadvantage if a cholangiogram had not been performed. Phillips[4] calculated that if one severe bile duct injury is prevented in every 1000 cholecystectomies, the cost of all 'unnecessary' cholangiograms is saved. This calculation does not include either the personal tragedy endured by the patient, or the costs associated with diagnostic work-ups in patients with postoperative abdominal pain or those involved in treating patients with undetected bile duct stones.

The potential risks of ductal injury associated with overzealous efforts to perform intraoperative cholangiography have been highlighted by some authors[32]. However, in this study there were no complications caused by the cholangiographic procedure, and the authors consider it to be an essential component of laparoscopic cholecystectomy, making it possible to reduce the risk of injury and to recognize it if it does occur.

The incidence of postoperative bile duct leakage in this series was 0·6 per cent, and it was mainly (three of four) caused by cystic duct leakage. This incidence is similar to that following open cholecystectomy[33], although higher figures have been reported following laparoscopic cholecystectomy. To reduce the risk of postoperative cystic duct leakage, it is probably important to secure the cystic duct with a loop ligature instead of clips, especially in patients with a distended cystic duct. Endoscopic retrograde cholangiopancreatography is invaluable in the postoperative diagnosis of bile duct complications. When leakage occurs, it can usually be treated safely and efficaciously by endoscopic means[34,35].

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Completion pancreatectomy for surgical complications after pancreaticoduodenectomy

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Significant complications continue to occur in a minority of patients undergoing pancreaticoduodenectomy; these frequently have fatal consequences. Analysis of 458 patients undergoing the Whipple procedure in this institution from 1972 to 1994 revealed that 16 patients with malignant periampullary tumours (ampullary, eight; pancreatic, seven; bile duct, one), and one patient with chronic pancreatitis subsequently required completion pancreatectomy. Postoperative difficulties after pancreaticoduodenectomy and indications for re-exploration were multifactorial: leakage ($n = 8$), pancreatitis ($n = 7$), bleeding ($n = 1$), and a delayed report of cancer at the margin of the pancreatic transection ($n = 1$). Completion pancreatectomy was often difficult (mean operating time 2·7 h, mean estimated blood loss 1897 ml). There was considerable significant postoperative morbidity (41 per cent) and mortality (24 per cent) after completion pancreatectomy. Patients who survived completion pancreatectomy lived a mean of nearly 4 years (range 4 months to 9·7 years, median 2·6 years). Tumour recurrence led to death in ten of 13 patients. Three patients remain alive and free of recurrence each more than 8 years after resection. Re-exploration and subsequent completion pancreatectomy after pancreaticoduodenectomy is rarely necessary, but if clinical manifestations occur secondary to failure of the pancreaticojejunostomy, early surgical intervention may maximize survival.

Although Kausch[1] first performed and Whipple *et al.*[2] subsequently popularized pancreaticoduodenectomy over 60 years ago, technical problems remain. The cumulative worldwide operative morbidity rate of over 25 per cent and mortality rate of approximately 10 per cent remain high[3,4]. While many patients tolerate pancreaticoduodenectomy well, and most tolerate pancreaticoduodenectomy with only minor complications there remains a large minority who develop significant complications – most importantly in the region of the pancreaticojejunostomy. Whether the operation itself is too taxing, the disease process too far advanced, or the surgical technique faulty remains unclear. Recent reports[5–7], including several from the authors' institutions[8,9], are encouraging, in that surgical progress is evident. As reports of improving results with the Whipple procedure are published, this operation may become more popular and the indications for its use may become liberalized. Only one published report is known which deals specifically with completion pancreatectomy for irreparable complications in or around the pancreaticoenterostomy[10]. This study reports experience in patients requiring completion pancreatectomy.

Methods

From a prospectively completed database of all patients who underwent a Whipple procedure ($n = 458$) at this hospital from 1972 to 1994, 17 patients were identified who underwent completion pancreatectomy (3·7 per cent) for postoperative difficulties. The medical records of these patients were reviewed, to determine patient demographics, presenting symptoms, preoperative management, operative indications and techniques for both the Whipple procedure and subsequent completion pancreatectomy, intraoperative fluid management, postoperative course after each procedure, hospitalization, morbidity and mortality rates, and overall long-term survival.

Results

Fifteen men and two women required completion pancreatectomy shortly after pancreaticoduodenectomy for adenocarcinoma of the ampulla ($n = 8$), pancreatic head ($n = 7$), or distal common bile duct ($n = 1$), and one patient with chronic pancreatitis. Patients' age ranged from 36 to 75 (mean 58, median 60) years. Jaundice (82 per cent), abdominal pain (41 per cent), and weight loss (27 per cent) were prominent findings on initial presentation. All candidates were considered fit for general anaesthesia and subsequent resection. There were three patients with insulin-dependent diabetes mellitus, three with evidence of mild renal insufficiency (serum creatinine more than 1·4 mg/dl), two with chronic pancreatitis, one with hepatic cirrhosis, and one with asthma severe enough to require steroid therapy. Physical examination revealed 12 jaundiced patients of which three were described as 'obese'.

Peak preoperative serum bilirubin levels ranged from 0·8 to 26·4 (mean 12·7, median 12·7) mg/dl. No patient was anaemic before surgery (serum haemoglobin: range 11·8–14·9 (mean 13·0, median 12·8) mg/dl). Seven patients had preoperative biliary decompression by endoscopic stenting ($n = 1$) or sphincterotomy ($n = 2$), operative drainage ($n = 3$), and percutaneous transhepatic stenting ($n = 1$). After these interventions serum bilirubin levels the day before pancreatectomy ranged from 0·6 to 22·3 (mean 6·0, median 3·7) mg/dl.

All Whipple procedures were performed by M.T. ($n = 10$) or directly under his supervision ($n = 7$) in a consistent manner previously described[9,11,12]. One deviation relevant to the pancreaticojejunostomy involved one patient where the interrupted inner layer of absorbable suture on the posterior wall was not used to protect and avoid stenosis or occlusion of a small, posteriorly placed pancreatic duct. Three of the Whipple procedures were described in the operative narrative as 'difficult' secondary to the degree of tumour involvement,

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Table 1 Operating time and intraoperative fluid management of 17 patients who had completion pancreatectomy after Whipple procedure

	Whipple			Completion pancreatectomy		
	Mean	Median	Range	Mean	Median	Range
Operative time (h)	6·1	6·1	4·8–7·3	2·7	2·4	1·3–4·0
Fluid input (ml)						
Blood	976	1000	0–3200	1291	1000	0–4800
Other	6635	5650	1500–12000	4472	4525	500–6800
Total	7611	6750	4700–14450	5763	5600	1200–10400
Fluid output (ml)						
Blood loss	1350	1000	250–3500	1897	1750	50–4800

Table 2 Bedside clinical findings crucial to the decision for relaparotomy following pancreaticoduodenectomy

Clinical findings	*n*
Tachycardia	8 (47)
Peritoneal irritation	7 (41)
Fever	7 (41)
Gastrointestinal bleeding	5 (29)
Abdominal pain	4 (24)
Changing deep drainage	3 (18)
Jaundice	2 (12)
Back pain	1 (6)
Dyspnoea	1 (6)
Total	16* (94)*

Values in parentheses are percentages *One patient was returned to the operating theatre for positive margins at the region of pancreatic transection

tissue friability, and/or patient obesity. The consistency of the pancreatic remnant was described as 'good' or 'strong' in three patients (one of whom included a resection margin involved by tumour on paraffin section). Tissue of the remaining gland was 'normal/soft' in 12 patients while two had tissue described as 'tenuous/friable'. Intraoperative consideration was given to total pancreatectomy which was decided against in these two instances. The length of operation and intraoperative fluid requirements are shown in *Table 1*.

Histological examination in six patients identified tumour within peripancreatic lymph nodes. One patient had pancreaticoduodenectomy with an uncomplicated hospital course for presumed complicated chronic pancreatitis. Subsequent histological identification of unsuspected ductal adenocarcinoma at the pancreatic margin necessitated elective completion pancreatectomy 14 days later.

In the remaining 16 patients, the decision to reoperate was often difficult (*Table 2*). Worrying evidence of clinical change (tachycardia, bloody drainage, fever, etc.) was identified from 6 h to 14 days (mean 6·1, median 7 days) after completion of the Whipple procedure. Bedside evaluation combined with routine laboratory studies and plain films of the abdomen or chest led to the decision to reoperate on all 16 patients. More involved studies were used selectively in 11 patients: abdominal computed tomography (CT) ($n=5$), abdominal ultrasonography ($n=5$), tube cholangiography ($n=4$), upper gastrointestinal endoscopy ($n=3$), upper gastrointestinal gastrografin study ($n=2$), angiography ($n=1$), and drain sinogram ($n=1$). The studies were of some merit in these patients by either excluding a source for intraluminal gastrointestinal bleeding or, more commonly, by identifying or excluding an abnormal collection of intra-abdominal fluid, anastomotic leakage, or pancreatitis of the remaining gland. Only seven (33 per cent) of these studies identified an abnormality (in six patients). CT found multiple abscesses in one patient and pancreatitis in another. Three of five ultrasonographic examinations showed multiple abscesses, splenic capsular haematoma, and excessive intra-abdominal fluid. Two cases of leakage at the pancreaticojejunostomy were identified by tube cholangiography.

Before completion pancreatectomy, two patients underwent invasive attempts to control anastomotic leakage: intraoperative suture repair of the pancreaticojejunostomy and percutaneous drain placement, respectively. Both attempts failed and completion pancreatectomy was performed 5 and 8 days later. Five patients were returned to the operating theatre without radiological or endoscopic examination. The decision to re-explore these patients was based on clinical grounds from a constellation of variable findings (*Table 2*) including the clinical need for aggressive fluid resuscitation. The time interval from the first worrying postoperative clinical findings to re-exploration was less than 24 h in nine of the 16 patients (median 18 h).

The precise indication for completion pancreatectomy and concomitant splenectomy was the presence of irreparable difficulties in or around the pancreaticojejunostomy: leakage ($n=8$), pancreatitis ($n=7$), bleeding ($n=1$), and positive surgical margins ($n=1$). The aetiology of this difficulty is not definitive, and may be somewhat arbitrary in that leakage, pancreatitis and bleeding are inter-related. At the time of re-exploration the jejunum, pancreas, and peripancreatic tissues were oedematous and friable (except for the elective completion pancreatectomy for positive surgical margins). Completion pancreatectomy and splenectomy was performed between 10 h and 30 days after completion of the Whipple procedure (mean 9·4, median 8 days). Although all re-explorations were deemed necessary and urgent, only four such completion pancreatectomies were performed outside elective surgical hours. M.T. performed 13 and supervised most completion pancreatectomies.

The subsequent early postoperative course was relatively uneventful for ten patients. However, three died from uncontrolled sepsis leading to multisystem organ failure after 2, 8 and 23 days, respectively. Additionally, one patient with cirrhosis died within 2 h of the

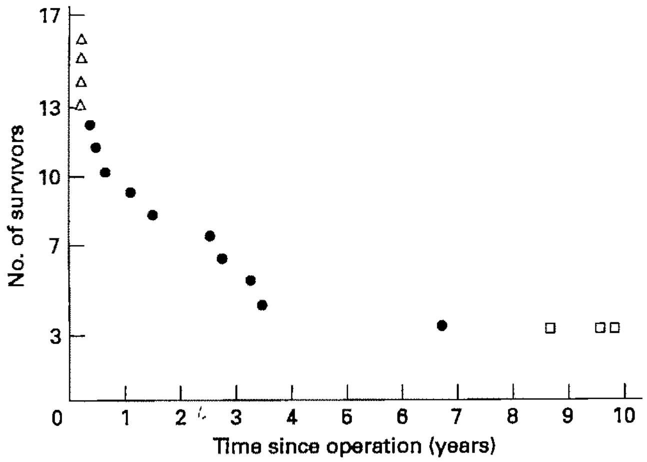

Fig. 1 Actual survival in 17 patients who underwent completion pancreatectomy after Whipple procedure. △, postoperative death; ●, died of tumour recurrence; □, alive

completion pancreatectomy secondary to coagulopathy and uncontrollable bleeding. Two additional patients required and tolerated a further abdominal exploration after completion pancreatectomy for bleeding from the jejunal mesentery (1 day after completion pancreatectomy), and for an intra-abdominal abscess (14 days after the procedure). A 56-year-old man underwent, without difficulty, a carotid endarterectomy for internal carotid artery stenosis causing transient ischaemic attacks during the postoperative period (21 days after completion pancreatectomy). Excluding the four deaths directly related to postoperative complications, the length of hospitalization from the date of first resection was a mean of 32 (range 16–55, median 30) days. Discharge from hospital occurred at a mean of 24 (range 13–42, median 19) days after completion pancreatectomy. All patients were insulin-dependent and under good diabetic control at discharge.

Of the 13 patients discharged from hospital, one patient developed severe gastrointestinal bleeding 1 month later, requiring urgent re-exploration and repair of a bleeding false aneurysm of the ligated splenic artery. An additional patient eventually underwent laparotomy and jejunojejunostomy to palliate small bowel obstruction secondary to local tumour recurrence at 11 months. Overall survival of the patients is shown in *Fig. 1*. Three patients with node-negative disease (ampullary, two; pancreatic, one) remain alive without recurrence nearly 10 years after operation. The rest died from tumour recurrence (range 4 months to 6·7 years). Three patients survived more than 2 years despite originally having node-positive pancreatic ductal cancer.

Discussion

While no surgeon revels in discussing, much less publicizing his or her complications, close scrutiny of these 17 patients among 458 who underwent Whipple resection between 1972 and 1994 identifies the importance of surgical technique and postoperative care in patients undergoing pancreaticoduodenectomy for cancer. The authors' analysis leads them to reaffirm three known surgical truisms: (1) the Whipple procedure demands meticulous surgical technique; (2) the decision to reoperate for complications is best made at the patient's bedside; and (3) completion pancreatectomy represents a major undertaking for both patient and extended surgical team.

Meticulous technique

Creation of a satisfactory pancreaticoenterostomy is one step among many that are necessary to perform a successful Whipple procedure. A repeatable, sound technique with attention to detail maximizes the chance of successful outcome. In all these patients, the authors strove to attain absence of tension at the suture line, no distal obstruction, an air- and water-tight seal, preservation of an excellent blood supply, and a patent anastomotic lumen. Assuming these five conditions were met, other causes for the failure of the pancreaticojejunostomy in 16 patients must be sought. These might include: inability of the pancreas to hold a suture; surgical trauma causing pancreatitis of the remnant; errors regarding precise suture placement and/or mobilization of the pancreas; and bleeding of the raw pancreatic or jejunal surfaces. Non-technical reasons might include hypotension for whatever reason that transiently caused poor perfusion of a healing pancreaticojejunostomy, and poor patient selection or the general lack of patient reserve to heal and recover from such a surgical 'insult'.

The answer is unclear, but probably multifactorial[13]. It is difficult to speculate using these retrospective data on the possible cause(s) for failure in these 16 patients. It is well documented that the firm gland of chronic pancreatitis holds suture well and the pancreaticoenterostomy is rarely problematic in Whipple procedures done for chronic pancreatitis[14]. During the study period 130 Whipple procedures were performed for pancreatitis at this institution, and only one required completion pancreatectomy. The other 16 cases of completion pancreatectomy represent 4·9 per cent of 328 Whipple procedures performed for malignancy. The operative narrative clearly states that 12 patients had a gland of normal or soft consistency, and two others were poorer still. Although not the first choice for resection of periampullary tumours, total pancreatectomy should be performed if the pancreaticoenterostomy is deemed unsatisfactory at operation. It is obvious that each step and every stitch of the pancreatic anastomosis is important.

In one study[10] pancreaticoduodenectomy for ampullary cancer resulted in completion pancreatectomy in 6 per cent of patients (five of 89) compared with 3 per cent of resections (six of 189) for pancreatic ductal lesions. The present study gives similar results: completion pancreatectomy was required in 8·3 per cent (seven of 84) of patients with ampullary cancer and 3·5 per cent (seven of 202) of patients with pancreatic lesions. This virtual doubling of the need for completion pancreatectomy with ampullary tumours may stem from the comparative rarity of pancreatitis with ampullary tumours, whereas such a response is common with pancreatic ductal adenocarcinoma. From these data it is difficult to make a case for traumatically induced pancreatitis, bleeding from the transected pancreas, or hypotension as consistently prominent causes for failure of the pancreaticojejunostomy. The same technique of mobilization, reconstruction, and haemostasis worked well in over 440 other Whipple's operations. Only one patient was hypotensive during surgery (systolic blood pressure less than 90 mmHg) or after surgery for a period longer than 10 min, and thus it is difficult to postulate hypotension as a cause of leakage at the anastomosis. Nine patients progressed to oral intake with the return of bowel function before a sudden clinical change up to 11 days after resection. Although the reasons for clinical deterioration appearing so late are unclear, it seems unjustified to change the routine of early ambulation and oral intake in all patients to attempt to eliminate this rare complication.

Bedside decisions

The decision to reoperate is often difficult, particularly early in the postoperative period. With the assortment of interventional techniques, parenteral nutrition, and pharmacological agents available, most patients with complications of pancreaticoduodenectomy can be treated without operation. However, Smith *et al.*[10] reported in a select group of complicated patients that delaying re-exploration with possible completion pancreatectomy may often lead to death. Seven of their 11 patients who required completion pancreatectomy at a mean of 18 days after pancreaticoduodenectomy did not survive. The authors hypothesized that re-exploration with the intent to eradicate sepsis and pancreatitis came too late for at least seven patients with systemic manifestations of sepsis leading to multisystem organ failure. While radiological or endoscopic examination is often invaluable in these complex cases, the studies should not be used to 'buy time' or delay the inevitable need to reoperate. Often the safest place for these patients with a constellation of symptoms and signs that can include tachycardia, fever, abdominal pain or distention is not the intensive care unit, nor the radiological or endoscopic suite, but the operating room. Enlisting the support and advice of others, including the radiologist or endoscopist may prove helpful, but it is the surgeon's good judgement at the bedside that must prevail. The decision to reoperate must rest on a thorough assessment of these critically ill patients at the bedside. When re-exploration and subsequent completion pancreatectomy appears indicated, it is best performed early, before systemic manifestations of the complications appear[15].

Completion pancreatectomy is a major undertaking

Of 458 patients, a total of 23 required re-exploration for difficulties after pancreaticoduodenectomy. Seventeen of this group (74 per cent) required completion pancreatectomy as a desperate means to salvage survival. Completion pancreatectomy is indeed a major surgical procedure requiring full support of the anaesthesia, blood bank, and intensive therapy teams. Technically the procedure may be demanding[10], but the greater challenge lies in the patient's ability to tolerate such major physiological challenges: massive fluid shifts, large blood loss, another general anaesthetic, immediate exocrine and endocrine pancreatic insufficiency, and some measure of immunological compromise due to splenectomy. Adhesions, oedematous tissue, loss of tissue planes, the technical need for splenectomy, vessel friability, peritoneal contamination, and patient instability may lead to a surprisingly difficult resection with large volume fluid requirements. Blood loss may actually exceed that of the previous pancreaticoduodenectomy (*Table 1*). Adequate resuscitation and preparation are imperative for success along with a full complement of surgical support staff on hand before embarking on exploration after pancreaticoduodenectomy.

Early re-exploration with completion pancreatectomy based on bedside decisions averted death in most patients with serious complications affecting the pancreatic remnant after pancreaticoduodenectomy. Long-term survival was not unlike patients completely free of severe complications and operative mortality[9]. Five-year survival for this group was 24 per cent. In fact, four patients with node-positive pancreatic ductal adenocarcinoma survived for a mean of 3·7 years. Three additional patients free of recurrence remain alive more than 8 years after resection. The authors therefore note that re-exploration need not be a preterminal event, rather it should be viewed as a rare, but often life-saving, necessary intervention on the road to recovery.

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Surgical workshop

Percutaneous removal of a 'bullet' from the liver

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Minimally invasive percutaneous procedures have progressed through adaptation of techniques from different specialties. Foreign bodies lodged in most areas have been retrieved successfully by the percutaneous route. Percutaneous transhepatic procedures, which began with cholangiography, have now progressed to include percutaneous cholangioscopy[1].

Case history

An 18-year-old man sustained a gunshot injury over the left side of the chest 1 year before admission to hospital. He underwent laparotomy, elsewhere, for removal of the bullet. Following this he developed a sinus, which discharged bile and pus from the right chest wall. Sinography and endoscopic cholangiography (*Fig. 1*) showed a foreign body to be in an abscess cavity communicating with the left hepatic duct.

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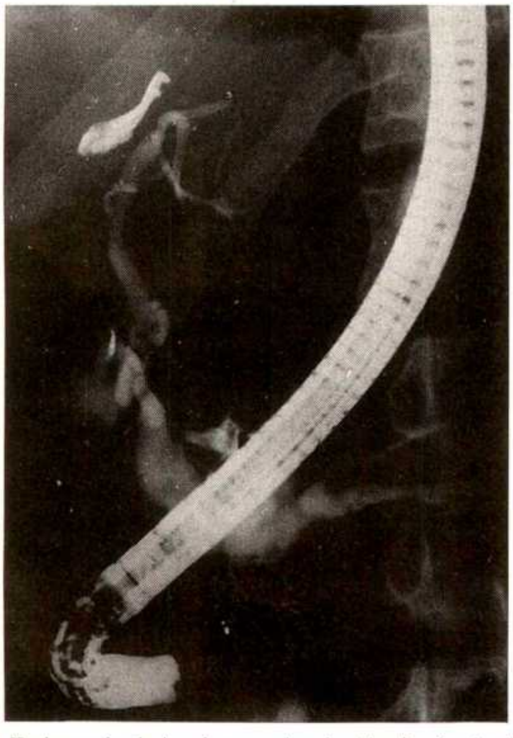

Fig. 1 Endoscopic cholangiogram showing the foreign body near the left hepatic duct

Surgical technique

Under general anaesthesia, using a C arm for radiological control, two floppy-tipped straight 0·97 mm guidewires were passed along the sinus tract up to the foreign body. Using serial Teflon (Du Pont, Stevenage, UK) dilators the tract was dilated to 18 Fr. Alken telescopic dilators were then used to introduce an Amplatz sheath. A 26-Fr nephroscope and sheath were introduced through the Amplatz sheath, using normal saline as irrigant. A total of 4 litres saline was used during the procedure. The foreign body was visualized and extracted with a triradiate grasper. A second fragment was also removed, with the same grasper. The endoscope was in the liver for 12 min. The foreign body was found to be the metal clip of a pen that the patient had had in his pocket at the time of the gunshot injury.

An 18-Fr Nelaton catheter was left in place and gradually removed over 5 days. After operation the discharge gradually reduced over 2 weeks.

Discussion

Percutaneous transhepatic access to the biliary system for dilatation of strictures, removal of gallstones[2–4], cholecystostomy[5], cholangioscopy[1], and insertion of stents and drains is a well established practice in interventional radiology. Dilatation of the access tract is usually achieved by placing serially larger cannulas over a few days to facilitate the introduction of larger instruments. This slow dilatation minimizes bleeding and infective complications[2,4].

In this case a pre-existing chronic fistulous tract facilitated dilatation and visualization of the foreign body and its extraction, with practically no bleeding. As fluid absorption is a known complication in such procedures, the outflow of irrigant and the central venous pressure were monitored throughout the procedure. Any excess absorption can be managed by a small dose of frusemide. There was no problem related to the size of the nephroscope.

The percutaneous approach to the biliary system for diagnostic and therapeutic purposes has an established role in hepatobiliary surgery. This technique was used successfully to remove a foreign body lodged in a relatively inaccessible location in the liver.

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Endoscopic drainage aborts endotoxaemia in acute cholangitis

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Forty patients with acute calculous cholangitis had successful endoscopic drainage. Bile from nasobiliary drains and venous blood was collected at 0, 12, 24, 36 and 48 h after endoscopy. Endotoxin levels were measured by the chromogenic Limulus Amoebocyte Lysate assay. There was a significant reduction in both bile and serum endotoxin levels after endoscopic drainage ($P < 0{\cdot}001$). Endotoxaemia occurred when bile endotoxin reached 10^3 EU/ml and rose exponentially beyond this threshold. Significant association was demonstrated between both bile and serum endotoxins to the clinical features of cholangitis ($P < 0{\cdot}05$). No correlation was evident between serum endotoxin and the parameters of white cell count, serum bilirubin and alkaline phosphatase ($r = 0{\cdot}53$, $0{\cdot}00$ and $0{\cdot}00$ respectively). Endoscopic drainage is effective in lowering bile and serum endotoxin levels and clinical signs and symptoms reliably predict endotoxaemia.

In 1877, Jean Martin Charcot[1] gave the first clinical account of acute cholangitis in which he described the triad of fever with chills and rigor, hepatic pain and jaundice. Reynolds and Dargan[2] in 1959 added that the triad was often accompanied by mental confusion and hypotension. These features together constitute the syndrome of acute obstructive cholangitis and carry a high mortality rate. Before the 1980s, treatment of severe cholangitis was surgical decompression. Endoscopic drainage has become the principal method of urgent biliary decompression. In this study, the effect of endoscopic drainage on endotoxin concentrations and their correlation with various clinical parameters was evaluated.

Patients and methods

Forty patients (19 men, 21 women), admitted to the Prince of Wales Hospital, Hong Kong with acute calculous cholangitis, were recruited for the study. Mean age was 66 (range 28–92) years. Patients with malignant obstruction or sepsis from intrahepatic cholelithiasis were excluded. Patients were managed with fluid resuscitation and intravenous antibiotics (ampicillin, cephalosporin and metronidazole) after blood cultures were taken. Complete blood counts, electrolytes, clotting profile and liver function tests were also done. Endoscopic drainage was performed within 36 h of admission. Blood pressure and pulse rate were monitored hourly and temperature taken every 4 h. The patient's mental state was recorded. Emergency drainage was indicated in patients with one of the following criteria: circulatory instability, mental confusion, persistent pain or high fever. Standard side-viewing duodenoscopes were used for endoscopy. Deep cannulation of the common bile duct was effected and bile aspirated to decompress the biliary system. A nasobiliary drainage catheter (ENBD-6.5-Leung; Wilson Cook Medical, Winston, USA) was then passed over a guidewire. Aspirated bile was stored in pyrogen-free polypropylene tubes, and also sent for culture. Serial bile samples were collected at 12, 24, 36 and 48 h from the nasobiliary drains. Venous blood was collected aseptically at the corresponding time intervals and stored in pyrogen-free heparinized tubes. Endotoxin assays were performed on these bile and serum samples.

Chromogenic Limulus Amoebocyte Lysate assay

The chromogenic Limulus Amoebocyte Lysate (LAL) assay system (Whittaker Bioproducts, Walkersville, Maryland, USA) contains a chromogen substrate, LAL and a reference endotoxin. Samples were initially diluted ten times with pyrogen-free water and heated to 75°C for 5 min to inactivate LAL inhibitors. Diluted bile or plasma 50 μl was mixed with reconstituted LAL 50 μl in sample wells of a sterile microtitre plate (Falcon 3072; Becton Dickinson, Lincoln Park, New Jersey, USA) at 37°C for 10 min. After incubation for another 10 min, the chromogen substrate 100 μl (Ac-Ile-Glu-Gly-Arg-*p*-nitroanilide, 1·6 mmol/l) was added to the sample well. After a further 6 min of incubation, 50 per cent (v/v) acetic acid 50 μl was added to stop the chromogenic reaction. Absorbance of each microtitre well was read at 405–410 nm with a DynaTech MR 600 microplate reader (DynaTech Laboratories, Chantilly, Virginia, USA).

All determinations were carried out in duplicate and two water blanks were run in parallel with each test. Endotoxin standards at concentrations of 0·1, 0·25, 0·5, 0·75 and 1·0 endotoxin units (EU) per ml were prepared from the reference endotoxin provided (*Escherichia coli* 0111:B4). Twelve EUs are equivalent to 1 ng of *E. coli* 0111:B4 lipopolysaccharide.

Statistical calculations were conducted with the Statistical Package for Social Sciences (SPSS; Chicago, Illinois, USA). Statistical tests used included the Kruskal–Wallis analysis of variance (ANOVA) test and Pearson's linear regression analysis.

Results

All patients had successful endoscopic drainage; 19 had nasobiliary drains alone, 21 had sphincterotomy and nasobiliary drain insertion. At endoscopy, a bulging oedematous papilla was seen in 11 patients indicating calculous impaction at the lower end of the common bile duct. Four patients had previous endoscopic sphincterotomy and one had surgical sphincteroplasty; another had spontaneous choledochoduodenal fistula. Two patients developed minor sphincterotomy haemorrhage; no major complication was recorded. One patient died. A 34-year-old woman with previous endoscopic sphincterotomy presented with recurrent calculous obstruction. There were signs of mental confusion and hypotension before endoscopy and the patient succumbed from overwhelming sepsis 6 h later despite successful nasobiliary drainage.

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Effect of endoscopic drainage on serum and bile endotoxin level

Bile endotoxin levels decreased dramatically following endoscopic drainage (*Fig. 1a*), especially in the first 24 h. Some 19 patients had detectable serum endotoxin initially which also fell following endoscopic drainage (*Fig. 1b*).

Relationship between bile and serum endotoxin level and clinical symptoms

Bile endotoxin levels at the time of endoscopic drainage and thereafter were plotted against the respective serum endotoxin levels (*Fig. 2*). Bile endotoxin levels were plotted on a logarithmic scale. No endotoxin was detected in serum when bile endotoxin was less than 10^3 EU/ml. After the bile endotoxin concentration exceeded 10^3 EU/ml, endotoxin began to appear in serum. Serum endotoxin rose exponentially with increasing bile endotoxin above 10^3 EU/ml.

Patients' clinical signs and symptoms with specific reference to Charcot's triad were documented in their records. Hypotension was defined as systolic blood pressure lower than 90 mmHg before endoscopy. Fever was defined as temperature higher than 37·8°C. Twelve patients showed only one of the three parameters. Fourteen patients presented with two parameters, while another 14 had the full triad. In the latter group, two patients developed mental confusion and hypotension (the Reynold pentad). Mean bile and serum endotoxin levels were significantly higher as the number of positive parameters of the triad increased (*Fig. 3a* and *b*). Mean bile and serum endotoxin levels in the two patients who manifested the Reynold pentad were double those of the group with full Charcot's triad.

Correlation between serum endotoxin level and biochemical parameters

Regression analyses were performed between serum endotoxin level at endoscopy, and white cell count, serum bilirubin and alkaline phosphatase levels. Thirty patients had raised white cell counts before endoscopy while 31 patients had a raised alkaline phosphatase level. Thirty-three patients had a raised serum bilirubin concentration and 26 had a bilirubin level of more than 50 g/dl. However, no correlation existed between serum endotoxin level, and serum bilirubin or alkaline phosphatase levels. There was some correlation evident between serum endotoxin level and white cell count with a Pearson's coefficient of 0·56. A very high white cell count indicated suppuration and endotoxaemia in some cases; however, endotoxaemia also occurred in patients with normal white cell counts.

Bacteriology

Positive bile culture was confirmed in 35 patients, and the predominant organisms isolated were *E. coli* and *Enterobacter* sp. The majority comprised a mixed growth. Positive blood culture was confirmed in 12 patients with pure growth of *E. coli*; endotoxaemia was detected in 28 patients.

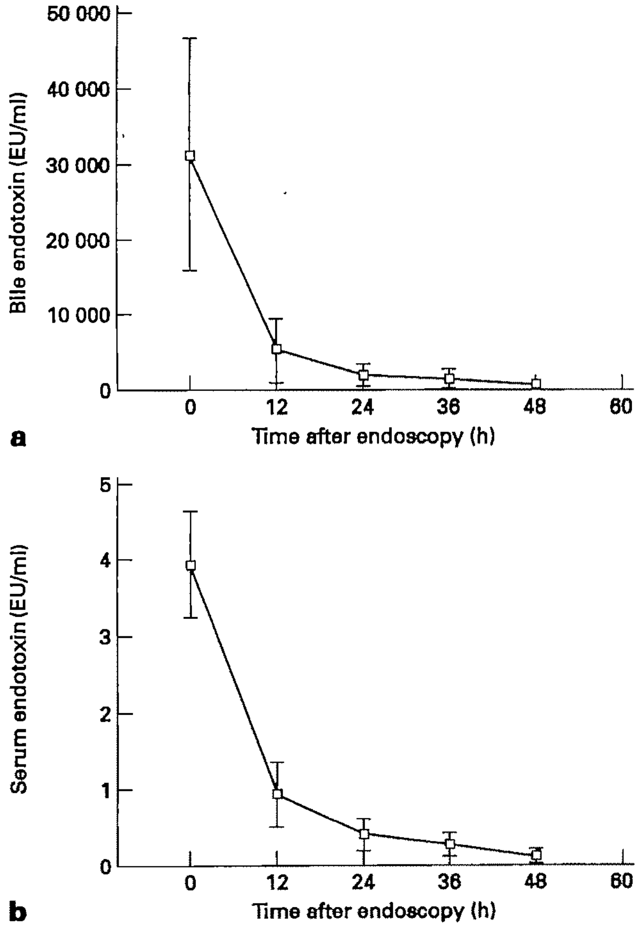

Fig. 1 Effect of endoscopic drainage on **a** mean(s.e.m.) bile endotoxin level, and **b** mean(s.e m.) serum endotoxin level in acute calculous cholangitis. EU, endotoxin units

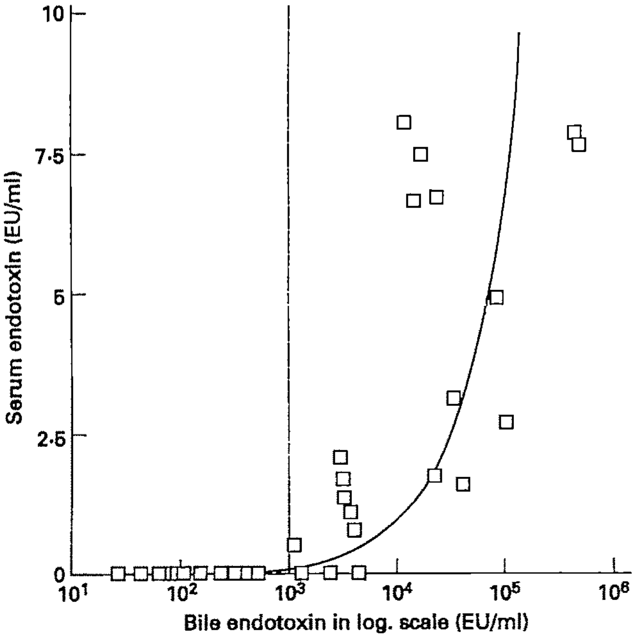

Fig. 2 Relation between bile and serum endotoxin concentrations. EU, endotoxin units

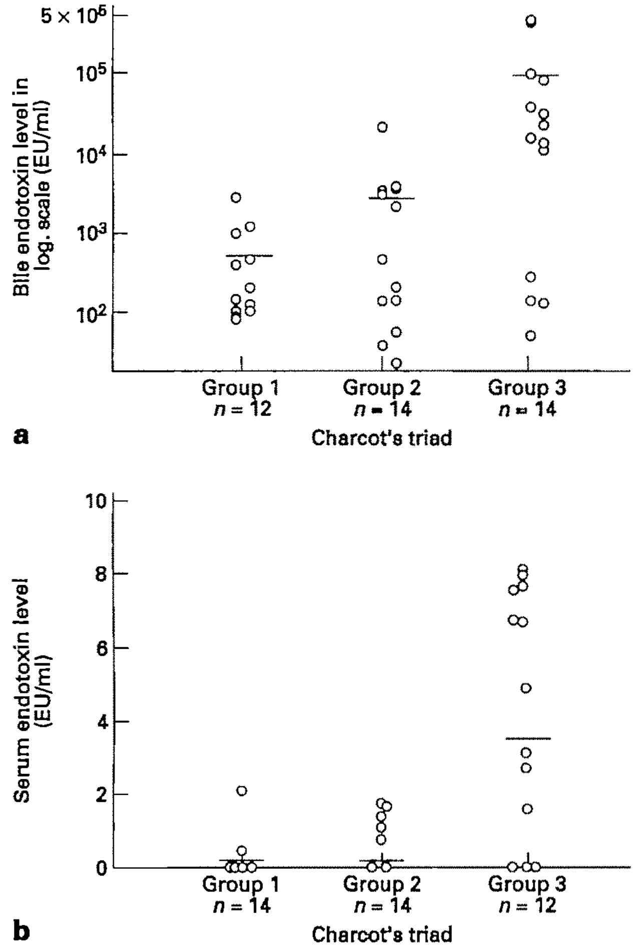

Fig. 3 Association between Charcot's triad and **a** bile endotoxin level, and **b** serum endotoxin level. Group 1, one parameter of Charcot's triad manifested; group 2, two parameters manifested; group 3, full triad manifested. $P < 0.05$ (Kruskal–Wallis ANOVA test)

Discussion

Therapeutic endoscopy has revolutionized the management of acute cholangitis. In other series by the authors[3], the efficacy of endoscopic drainage was demonstrated by successfully treating 97 per cent of 105 patients with acute calculous cholangitis who did not respond to conservative management. The mortality rate was only 4·7 per cent. Leese *et al.*[4] retrospectively reviewed the management of 94 patients with acute cholangitis. The mortality rate in patients who had endoscopic drainage was lower than that of those who had surgical decompression. In the present study, endoscopic drainage dramatically reduced bile and serum endotoxin levels, which confirmed a clinical impression that endoscopic drainage aborts endotoxaemia.

How endoscopic drainage works in aborting endotoxaemia in cholangitis remains conjectural. The principal determinant is believed to be lower biliary pressure. The association between biliary pressure and bacteraemia has been documented in both canine and human studies; bacteraemia occurred when biliary pressure exceeded 20 cmH_2O. Biliary pressures of 30 cmH_2O or more were found in patients with suppurative cholangitis from calculous impaction[5–8]. There has been no report on the relationship between biliary pressure and endotoxaemia. The authors attempted to measure biliary pressure endoscopically in patients before and after drainage by connecting the nasobiliary drain to a variable pressure volumetric pump (model 560; IVAC, San Diego, California, USA), but the technique was difficult in acute obstruction and disimpaction of stones during cannulation or precut sphincterotomy often led to spontaneous loss of biliary pressure. There was a universal trend of lower biliary pressure following drainage.

It has been shown that the hepatocyte secretory pressure is 30 cmH_2O[9]. When hydrostatic or biliary pressure exceeds hepatocyte secretory pressure, bile excretion ceases. There is retrograde flow of biliary tree contents into sinusoidal spaces under high biliary pressure; this is possibly the mechanism of endotoxaemia. When biliary pressure is lowered, bile excretion returns and the reflux of endotoxin, or indeed bacteria, into the systemic circulation stops.

Endotoxaemia can also be explained by the interruption of endotoxin metabolism. Endotoxin is usually cleared by Kupffer cells in the liver and passed to hepatocytes to be excreted in bile[10]. With obstruction, bile flow and therefore excretion diminishes, leading to overwhelming of the Kupffer cell system by endotoxin. The relationship between bile and serum endotoxin levels shown in the present study may explain this phenomenon. The threshold in bile endotoxin may reflect the concentration at which the Kupffer cell system becomes saturated.

The correlation between endotoxaemia and the clinical course of patients has not been well documented. Brandtzaeg *et al.*[11] showed that initial plasma endotoxin level in patients with systemic meningococcal disease correlated with shock and subsequent mortality. The authors found an association between the severity of cholangitis and both the initial bile and serum endotoxin levels. Patients with Reynold's pentad had the highest endotoxin level followed by those with Charcot's triad. The initial endotoxin level has predictive value in the severity of cholangitis. These findings highlight the importance of clinical signs and symptoms in predicting endotoxaemia. White cell count, serum alkaline phosphatase and (surprisingly) serum bilirubin levels showed no correlation with serum endotoxin level. A high serum bilirubin concentration was believed to characterize the most toxic group of patients but this could not be confirmed. While high serum bilirubin or alkaline phosphatase levels may indicate the diagnosis and a longer duration of obstruction, they need not necessarily be raised in acute obstruction, and did not correlate with the severity of endotoxaemia in this study. The practice of relying on patients' signs and symptoms in determining the need for urgent endoscopic drainage seems justified. Significant signs include circulatory instability, mental confusion, persistent pain or high fever.

Endotoxaemia is not synonymous with bacteraemia. In this series, endotoxin was detectable in serum in 28 patients but only 12 had a positive culture. The most obvious source of endotoxin in serum is Gram-negative bacilli. In suppurative cholangitis, it is believed that a significant proportion of endotoxin arises from seepage through junctions between bile canaliculi and sinusoidal spaces into the systemic circulation under high biliary pressure, without intercurrent bacteraemia. The interruption of endotoxin metabolism adds to the problem. In patients with sepsis, intestinal endotoxaemia is well documented, although its contributory role is uncertain[12]. The use of intravenous antibiotics may also play a role in the discrepancy between endotoxaemia and bacteraemia. Endotoxin, a component of the bacterial cell wall, is released into the circulation as a result of bacterial lysis induced by antibiotics or cell-mediated immunity. The level of endotoxin activity may be a more appropriate measurement of pathogenic activity than quantitative assay of bacteria. Moreover, bacterial species exhibited different endotoxin activities and the majority of bile cultures yielded mixed growths.

The findings of the present study confirm the clinical impression that endoscopic drainage aborts endotoxaemia in acute cholangitis. Clinical signs of cholangitis predict endotoxaemia and can dictate the need for urgent endoscopic drainage.

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Surgical workshop

Management of hepatic duct injury during hemihepatic vascular occlusion

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Hepatocellular carcinoma can occur in patients with cirrhosis, and limited hepatic resection may be the treatment of choice[1]. Hemihepatic vascular occlusion is one of the techniques used to reduce blood loss during resection of cirrhotic liver. It has the advantage of preserving blood flow to the contralateral lobe of the liver[2]. Alternative techniques are inflow occlusion (Pringle manoeuvre) and total vascular isolation[3,4]. The separate division of the hepatic artery, portal vein and hepatic duct within the Glissonian pedicle in a cirrhotic liver often leads to excessive bleeding and lymphorrhoea due to portal hypertension. Thus, encirclement of the entire Glissonian bifurcation is a preferred technique to resect a liver with cirrhosis[5]. Control of the hemihepatic inflow pedicle can sometimes be difficult[5] since vessels to the caudate lobe can be torn or the hepatic duct can sustain injury.

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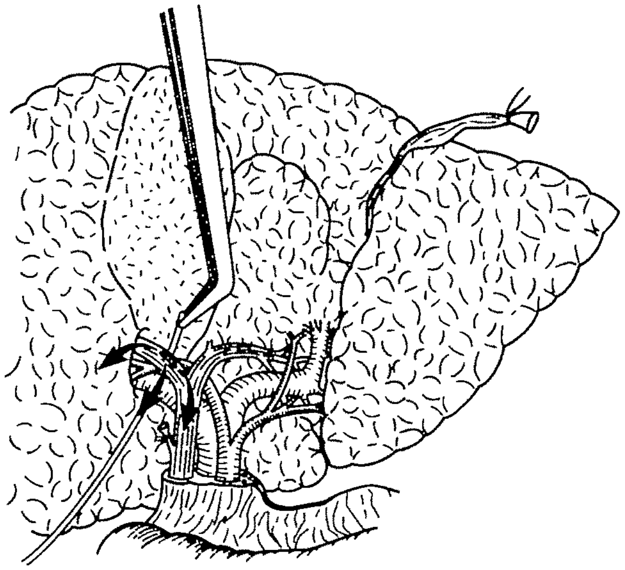

Fig. 1 Hepatic duct injury during dissection of the Glissonian bifurcation, resulting in a longitudinal tear on the duct

Surgical technique

Following cholecystectomy the Glissonian bifurcation is bluntly dissected away from the quadrate lobe and a right-angled forceps is carefully inserted along the Glissonian sheath toward the vertical aspect of the caudate lobe. At this point, tributaries to the caudate lobe may be injured by surgeons with limited experience (*Fig. 1*). Bleeding from a small vessel can be controlled by packing oxidized cellulose (Oxycel; Becton Dickinson, Franklin Lakes, New Jersey, USA). Bile duct injury, often longitudinal, can be a serious problem in the presence of liver cirrhosis, and leakage of bile is often associated with intraperitoneal septic complications.

Even when such a bile duct injury is identified, direct surgical repair is difficult since the hepatic duct is located deep in the cirrhotic hepatic parenchyma. Sutures on the small hepatic duct may cause stricture or obstruction.

To manage a longitudinal tear of the small hepatic duct during hemihepatic vascular control of a cirrhotic liver, a T tube is inserted via a short choledochotomy; the tear is then sealed with fibrin adhesive (Beriplast P; Behringwerke, Marburg, Germany) Bile flow in patients with external drainage or a T tube follows the path of the least resistance. The fibrin adhesive allows for external splinting of the damaged duct by reducing biliary pressure. The T tube is removed 3 weeks after operation, after confirming the absence of leakage or stricture by T tube cholangiography.

Discussion

This technique was used in three patients with non-alcoholic cirrhosis. There were no biliary complications, including stenosis or obstruction of the bile ducts, during 18, 24 and 63 months of follow-up.

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Choledochal cysts – differences in children and adults

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Choledochal cysts in children and adults may behave differently. To identify these differences the records of 49 patients (22 children and 27 adults) who underwent surgery for choledochal cysts over a period of 7 years were analysed retrospectively. In two adult patients who had undergone a previous cholecystectomy an acquired malformation could not be excluded. Cholangitis was more common in adults. Choledochal cysts in children were predominantly Type I cystic lesions, whereas Type IV cysts were more common in adult patients. Anomalies of the pancreatic duct and associated hepatobiliary problems were seen exclusively in adults and the latter can make excision of the cyst more difficult and complicated. To prevent the development of complications choledochal cysts should be excised as soon as they are detected.

Choledochal cysts are uncommon lesions and it is estimated that such malformations occur in one of 100 000–150 000 live births, three to four times more frequently in females[1,2]. Although the majority of these patients present in infancy and childhood, about 20–30 per cent of patients are diagnosed as adults[2,3]. Choledochal cysts in adults may have complex clinical and pathological characteristics that influence the surgical management and outcome[4]. During the 7 years from 1987 to 1994 the authors treated 49 patients with choledochal cysts (22 children and 27 adults). These two groups were studied to identify the differences in clinical presentation, morphology, associated hepatobiliary problems and the effect of these on surgical management.

Patients and methods

Forty-nine patients underwent surgery for choledochal cyst between April 1987 and April 1994 at the authors' hospital. The diagnosis of choledochal cyst was based on the characteristic radiological features and operative findings. Cysts were grouped according to Todani and colleagues'[5] modification of the Alonso-Lej classification: Type I, solitary extrahepatic cyst, Type II, extrahepatic supraduodenal diverticulum; Type III, choledochocele; Type IVa, extrahepatic and intrahepatic cysts; Type IV, multiple extrahepatic cysts; and Type V, Caroli's disease. The records of these patients were reviewed and all were regularly followed.

Statistical methods

Fisher's exact test was used for statistical analysis $P < 0{\cdot}05$ was considered significant.

Results

There were 41 female and eight male patients. Twenty-two patients were children aged between 6 and 12 years, and 27 were adults (over 12 years), aged between 15 and 70 years. In the group of children, presenting symptoms were intermittent abdominal pain in 20 and jaundice in six. Two patients had a history of intermittent fever and pain associated with jaundice, suggestive of cholangitis. Four patients had a palpable abdominal mass, although the classical triad of pain, jaundice and abdominal mass was seen in only three. Adult patients presented most commonly with biliary pain (24) and a history of jaundice (19). Sixteen patients had had cholangitis and two had symptoms of recurrent pancreatitis. Only one patient had a palpable abdominal mass and three had hepatomegaly. Five patients in the adult group had undergone cholecystectomy for gallstone disease between 5 months and 10 years before admission. Exact information about the status of the bile duct during cholecystectomy was not available in three patients and in two an operative cholangiogram was reported as normal. Nine patients in the adult group had already undergone drainage operations for their choledochal cysts between 6 months and 9 years earlier: three had had external drainage of the cyst, four had cystojejunostomy and two cystoduodenostomy. All patients presented with episodes of cholangitis and two had developed portal hypertension.

Ultrasonography was the initial diagnostic procedure in all patients followed by endoscopic retrograde cholangiopancreatography (ERCP). Type I choledochal cysts were more common in children than adults (18 of 22 *versus* 15 of 27) ($P < 0{\cdot}05$), and Type IV cysts were seen more often in adults than children (12 of 27 *versus* 4 of 22) ($P < 0{\cdot}05$) (*Table 1*). Intrahepatic cysts in the two groups were apparent in both lobes of the liver. Information about the pancreatic duct was available in 16 children and 18 adults. Abnormal pancreatic bile duct junction was seen in seven children and eight adults. Abnormalities of the pancreatic duct were apparent only in adult patients; four patients showed dilatation of the pancreatic duct (range 8 mm–1·4 cm) (*Fig. 1*) and two of these had intraductal pancreatic calculi (*Fig. 2*). Cystolithiasis was seen in eight adults, five of whom had undergone a previous drainage operation. Five adult patients had gallstones and two had cholangiolitic liver abscesses in the left lobe of liver. In one adult patient there was malignancy in the choledochal cyst.

All patients underwent surgery. Excision of the extrahepatic cyst and Roux-en-Y hepaticojejunostomy were carried out in all 22 children and 24 adult patients. In three adults the cyst could not be excised. One patient had malignancy in the cyst, one patient who had

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Table 1 Type of choledochal cyst

Cyst type	Children	Adults
I	18	15
Cystic	17	9
Cylindrical	1	6
II	0	0
III	0	0
IVa	4	11
Cystic*–cystic†	4	3
Cystic*–cylindrical†	0	3
Cylindrical*–cylindrical†	0	5
Cylindrical*–cystic†	0	0
IVb	0	1

*Extrahepatic cyst; †intrahepatic cyst

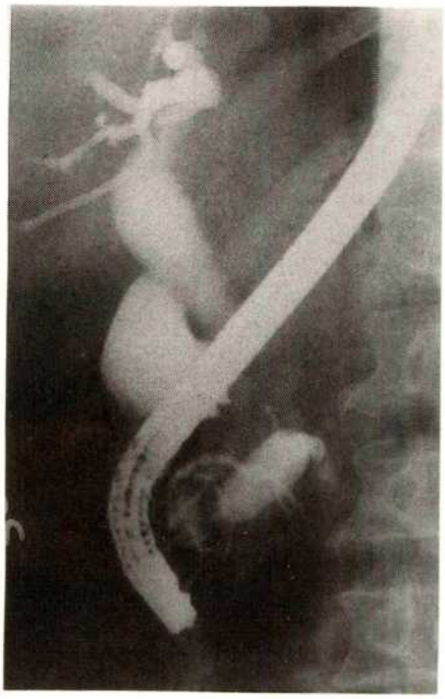

Fig. 1 Endoscopic retrograde cholangiopancreatography of choledochal cyst with dilated pancreatic duct

undergone cystoduodenostomy previously developed portal hypertension, and one elderly patient who had dense vascular adhesions between the cyst, liver and duodenum developed arrhythmias during surgery; the proposed excision of the choledochal cyst was abandoned. A wide cyst–jejunal bypass was done in these three patients. There were no deaths during surgery and no significant postoperative complications. Bile cultures taken during surgery were sterile in 20 children, but 13 adults had positive bile cultures, the common organisms being *Escherichia coli*, *Klebsiella* sp. and streptococci.

Follow-up ranged from 2 months to 6 years. Two adults with Type IVa cystic lesions (both in the extrahepatic and intrahepatic bile ducts) had recurrent cholangitis despite a patent bilioenteric anastomosis demonstrated by hepatoiminodiacetic acid scanning. Of the eight patients with cylindrical dilatation of the intrahepatic ducts, significant regression of the cyst size was seen in five patients on ultrasonography 8–16 months after excision of the extrahepatic component.

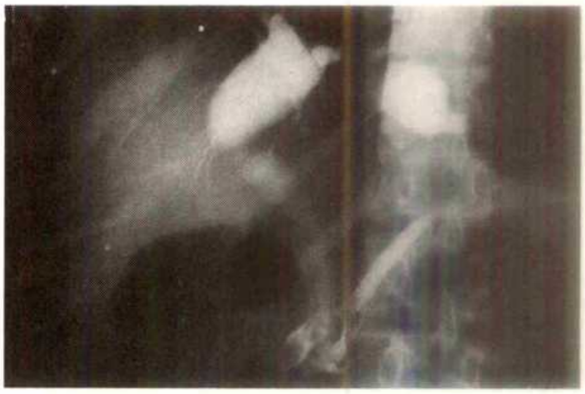

Fig. 2 Endoscopic retrograde cholangiopancreatography of choledochal cyst with dilated pancreatic duct and stones in the proximal pancreatic duct

Discussion

Choledochal cysts present more commonly in infancy and childhood although the condition may be diagnosed for the first time in adulthood. As the authors' hospital is primarily a referral centre for adults, the majority of patients with choledochal cysts in this series were adults. Choledochal cysts are believed to develop because of the combined effect of weakness of the bile duct wall and an increased intraluminal pressure secondary to obstruction of the distal bile duct which is usually congenital but may be acquired. Two adult patients in this series who had normal bile duct at operative cholangiogram performed during cholecystectomy subsequently developed choledochal cysts. Schmid *et al.*[6] reported similar findings in some of their patients, suggesting an acquired aetiology in such patients.

Symptoms of choledochal cysts are characteristically intermittent but progressive. Both children and adults present with abdominal pain and jaundice. Cholangitis in the authors' experience was more common in adults (16 *versus* two patients); this may be related to the fact that 14 of these adult patients had had previous biliary surgery which could have been responsible for cholangitis. Pancreatitis is seen more often in adult patients, and occasionally it can be the only presenting symptom as was the case with two adult patients in this series. In adult patients an abdominal mass is usually not palpable and the classical triad of jaundice, pain and right upper quadrant abdominal mass was seen in only three children in this series. Tan and Howard[7] reported the classical triad of presentation in 24 per cent of their patients and, in contrast to the findings of the present study, this occurred more frequently in adults than children.

The authors found that Type I choledochal cyst was the most common type of cyst in both children (18 patients) and adults (15), Type IV cysts being more common in adults (12) than children (4). It has been reported that cylindrical dilatation of the extrahepatic ducts is rare[8]; in the authors' experience this was true for children but in adults such dilatation is common. Seventeen Type I cysts in children were cystic, whereas in adults only nine were cystic, the remaining five being cylindrical. Intrahepatic cysts in all children with Type IVa cysts were cystic, suggesting a basic developmental defect. In adult patients with cylindrical dilatation of the extrahepatic duct, the intrahepatic cysts were always cylindrical, whereas in patients with cystic dilatation of extrahepatic ducts intrahepatic cysts were either cystic or cylindrical. Cylindrical dilatation of intrahepatic ducts may be secondary to biliary obstruction and has been seen to regress after excision of the extrahepatic component. This occurred in five patients in this study during follow-up of between 8 and 18 months.

Anomalies of the pancreatic duct were recognized at ERCP in the adult patients suggesting that choledochal cysts in this group represent an anomaly of the entire pancreaticobiliary system rather than just the biliary tract[9]. Four adult patients in this series showed dilatation of the pancreatic duct with intraductal calculi in two; similar changes were reported by Rattner *et al.*[9]. Abnormal pancreatic bile duct junction in both children and adults was seen in approximately 44 per cent. Komi *et al.*[10] proposed a new classification of the abnormal pancreatic bile duct junction, which could probably influence the type of surgical procedure needed for choledochal cyst.

Hepatobiliary problems such as cystolithiasis, cholelithiasis, secondary biliary cirrhosis, and cholangiolitic liver abscesses reflecting the effects of prolonged stasis and infection are seen mainly in adults. Calculi in the cyst are common; eight adult patients in this series had cystolithiasis. These calculi are more likely to occur in patients with persistent biliary symptoms after enteric drainage operations (five in the present study). Calculi in the intrahepatic cysts, although less common, are more prone to cause complications such as cholangitis and liver abscess. Two adult patients had liver abscess associated with calculi in the intrahepatic duct. In children, associated problems are reported to be developmental in nature, such as the presence of a double gallbladder, congenital hepatic fibrosis and annular pancreas[11]. Portal hypertension in patients with choledochal cysts may occur either because of secondary biliary cirrhosis or direct compression by the cyst[12,13], and has been reported both in infancy and adults. Two adult patients in the present series had portal hypertension secondary to biliary cirrhosis; both had undergone cystojejunostomy earlier. Patients attending for cyst excision after previous drainage operation are at greater risk of developing portal hypertension and should be carefully evaluated.

Choledochal cysts, whether in children or adults, are best managed by total excision to prevent cholangitis and malignant change. Internal drainage of cysts as recommended in the past has been associated with a high incidence of complication such as stricture[3]. Nine adult patients in this series presented with recurrent jaundice and cholangitis following drainage procedure performed previously. Cyst excision was possible in eight of these patients, and could not be done in one patient with portal hypertension. Excision of a large choledochal cyst can be technically challenging in some adult patients because of the presence of cholangitis, portal hypertension, or previous internal drainage procedure having been performed. The technique described by Lilly[14] of leaving the posterior wall of the cyst intact to prevent injury to the portal vein is useful in such situations. Complete excision is not possible in cysts which have an associated intrahepatic component unless the intrahepatic cysts are confined to one lobe of liver. Surgery in these patients is aimed at excision of the extrahepatic part of the cyst and the creation of a wide stoma to provide free drainage of bile from the liver to the intestines. The hepaticojejunostomy stoma can be widened by an incision along the lateral wall of both transected ducts[15]. Ohi *et al.*[16] recommend the removal of not only the extrahepatic cyst but also the area of relative stenosis between the common hepatic duct and the intrahepatic bile duct cyst to achieve free drainage from inside the liver. In contrast to patients with Type I choledochal cysts where excision of the cyst gives good results, patients with Type IVa cysts can have problems even after excision of the extrahepatic cyst due to bile stasis and infection in the remaining intrahepatic cysts (especially of the cystic type). These patients may develop recurrent cholangitis, intrahepatic stones and rarely malignancy. Close follow-up is therefore necessary[17,18].

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Bradykinin antagonists HOE-140 and CP-0597 diminish microcirculatory injury after ischaemia–reperfusion of the pancreas in rats

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Ischaemia–reperfusion of the pancreas was performed in 35 anaesthetized Sprague–Dawley rats. The effects of two bradykinin antagonists, HOE-140 (13 μg kg^{-1} intravenous bolus injection, $n = 7$) and CP-0597 (18 μg kg^{-1} h^{-1} intravenous infusion, $n = 7$) on pancreatic microvascular perfusion and leucocyte–endothelium interaction were quantitatively analysed by intravital fluorescence microscopy. Three further groups underwent sham operation ($n = 7$), ischaemia of 2 h without treatment ($n = 7$), and ischaemia of 2 h with infusion of phosphate buffer ($n = 7$). Functional capillary density was significantly greater in animals treated with HOE-140 or CP-0597 than in sham-treated animals, and was decreased to only 60 per cent. Adherence of leucocytes to the endothelium of postcapillary venules was significantly reduced when compared with ischaemia without antagonist. These results demonstrate a positive effect of the two bradykinin antagonists HOE-140 and CP-0597 on microvascular perfusion failure after ischaemia–reperfusion of the pancreas.

Activation of bradykinin through the action of kallikreins, which are present in several tissues including the pancreas[1], mediates acute inflammation with increase of microvascular permeability, vasodilatation and leucocyte migration and accumulation[2–5]. These findings suggest involvement of the kallikrein–kinin system in the inflammatory process of acute pancreatitis[3].

Ischaemia–reperfusion injury of the pancreas is thought to be a causative factor in the pathogenesis of acute pancreatitis and is characterized by microvascular perfusion failure, increase of microvascular permeability and enhanced leucocyte–endothelium interaction in postcapillary venules[6–13]. These changes in microvascular perfusion are present soon after induction of experimental acute pancreatitis, and impairment of pancreatic microcirculation correlates with the severity of this disease[14,15].

The aim of this study was to investigate the influence of two bradykinin antagonists (HOE-140 and CP-0597) on pancreatic microvascular perfusion failure and enzyme release after complete ischaemia–reperfusion of the pancreas in rats. The extent of injury to the microcirculation was assessed by intravital fluorescence microscopy.

Materials and methods

Surgical procedure

The animal model of ischaemia–reperfusion of the pancreas has been described in detail elsewhere[16]. Thirty-five adult male Sprague–Dawley rats (Charles River, Sulzfeld, Germany) weighing 210 ± 15 g were used after overnight fasting with free access to water. Ether-induced anaesthesia was followed by intraperitoneal injection of chloral hydrate (36 mg per 100 g body-weight) and maintained by intravenous injection of α-chloralose (Merck, Darmstadt, Germany) (5 mg per 100 g body-weight). After tracheotomy and intubation, the animals were mechanically ventilated to maintain arterial partial pressure of oxygen at 100–110 mmHg and arterial partial pressure of carbon dioxide in the range 35–40 mmHg. Polyethylene catheters were introduced into the right common carotid artery and jugular vein for continuous monitoring of arterial pressure, heart rate, central venous pressure (CVP), and for volume replacement (3–4 ml NaCl 0·9 per cent per h), injection of fluorescent compounds and administration of drugs.

After laparotomy the four arteries supplying the pancreas (gastroduodenal artery, left gastric artery, splenic artery and caudal pancreatoduodenal artery) were isolated from the surrounding tissue. To induce complete but reversible ischaemia of the pancreas these vessels were occluded with microvascular clips (Aesculap Yasargil Standard Aneurysm Clip, Temporary; Aesculap, Tuttlingen, Germany). After a period of ischaemia of 2 h, the clips were removed to allow reperfusion. Immediately afterwards the pancreas and spleen were exteriorized for intravital microscopy on an adjustable stage attached to the microscope and entirely covered by a thin transparent Teflon membrane to prevent drying. Sham-operated control animals underwent the same surgical procedure without vessel occlusion.

After a period of 30 min for stabilization the animals were randomly assigned to five groups: (1) sham group (sham operation, no ischaemia; $n = 7$); (2) ischaemia group (ischaemia 2 h; $n = 7$); (3) phosphate buffer group (ischaemia 2 h and continuous intravenous infusion of phosphate buffer 1·5 ml h^{-1} starting 15 min before the end of ischaemia; $n = 7$); (4) HOE-140 group (ischaemia 2 h and intravenous bolus injection of HOE-140 13 μg kg^{-1} (1·5 ml) 15 min before the end of ischaemia; $n = 7$) and (5) CP-0597 group (ischaemia 2 h and continuous intravenous infusion of CP-0597 18 μg kg^{-1} h^{-1} starting 15 min before the end of ischaemia, volume equivalent to that used in the phosphate buffer group; $n = 7$). The continuous infusion of drugs in groups 3 and 5 lasted for the entire period of reperfusion.

Pharmacological agents

The bradykinin antagonist HOE-140 (Hoechst AG, Frankfurt/Main, Germany) with a molecular weight of 1304·6 was dissolved in phosphate buffer. The peptide has the following sequence: H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH. The bradykinin antagonist CP-0597 (Cortech, Denver, Colorado, USA) with a molecular weight of 1292·5 was also dissolved in phosphate buffer. This has the following sequence: D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-N-Chg-Arg. Because of its short action (half-life estimated to be less than 1 min), CP-0597 has to

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be applied as a continuous infusion in the entire reperfusion period.

The macrohaemodynamic parameters (mean arterial pressure, heart rate and CVP) were monitored continuously during the entire experiment. The microhaemodynamic parameters were assessed at 30, 60 and 120 min after the onset of reperfusion.

Blood samples for determination of pancreatic amylase and arterial haematocrit were taken from the intra-arterial catheter. Serum pancreas α-amylase concentration was determined at the beginning and conclusion of each experiment using an enzyme–antibody solution (P-Amyl MPR 2; Boehringer, Mannheim, Germany). Arterial haematocrit was assessed at the beginning, after surgical preparation, at the end of ischaemia and at the end of the experiment. The animals were killed by an injection of pentobarbital.

Intravital fluorescence microscopy and quantification of microcirculation

After intravenous injection of 0·15 ml 0·75 per cent FITC–HES (hydroxyethylstarch (molecular weight 200 000) labelled with fluorescein isothiocyanate; Laevosan, Linz, Austria) for contrast enhancement of microvessels and 0·1 ml 0·2 per cent Rhodamine 6G (molecular weight 497; Sigma, St Louis, Missouri, USA) for *in vivo* staining of leucocytes, intravital microscopy of the pancreas was performed using a modified Leitz-Orthoplan microscope (Leitz, Wetzlar, Germany) with a mercury lamp (100 W, HBO) attached to a Ploemo-Pak illuminator with $I_{2/3}$ (excitation 450–490 nm, emission greater than 515 nm) and N_2 (excitation 530–560 nm, emission greater than 580 nm) filterblocks (Leitz) for epi-illumination. Use of a saltwater immersion objective (SW × 25/0·60; Leitz) allowed magnification of approximately × 800. The observations were recorded by means of a charge-coupled device (CCD) video camera (FK 6990; Cohu, Prospective Measurements, San Diego, California, USA) and stored on a video tape (video recorder AG-7330; Panasonic, Munich, Germany) for off-line evaluation.

Quantitative assessment of the microcirculation included determination of the functional capillary density (FCD) and leucocyte kinetics in postcapillary venules and was performed off-line using frame-by-frame analysis of the video tape images. The FCD of exocrine pancreatic tissue was determined after injection of FITC–HES as the length (cm) of nutritive capillaries perfused with red blood cells per observation area (cm^2) according to the method described by Schmid-Schoenbein *et al.*[17]. This entails superimposing a grid system (squared type) on the video screen with a defined length of the square within ten randomly selected areas per animal ($400 \times 300\,\mu m$). The number of intersections between perfused capillaries and grid allows calculation of capillary length per observation area. In addition, the index of capillary heterogeneity (distribution of local capillary density) was determined within these ten areas[18].

For quantification of leucocyte–endothelial interaction at least three postcapillary venules per animal with a diameter not larger than $40\,\mu m$ and length $150\,\mu m$ were selected at each observation time. For each time point identical venules were observed. Freely flowing (non-adherent) leucocytes were defined as cells that did not come into contact with the inner vessel surface within the focus level during the observation period. Adherent leucocytes (stickers) were defined as cells attached to the inner vessel surface for the entire observation period of 30 s[19], and are given as the number of cells per endothelial surface area (mm^2). The surface area was calculated using diameter and length of the given vessel segment (measured by superimposing a scale on the video screen assuming a cylindrical geometry[20]). Rolling leucocytes were defined as cells intermittently interacting with the endothelium for less than 30 s. The fraction of rolling leucocytes was calculated as a percentage of the freely flowing non-adherent cells and rolling cells.

Statistical analysis

Data are presented as mean(s.e.m.) and were tested for normal distribution. Analysis of variance (ANOVA) and Dunnett's

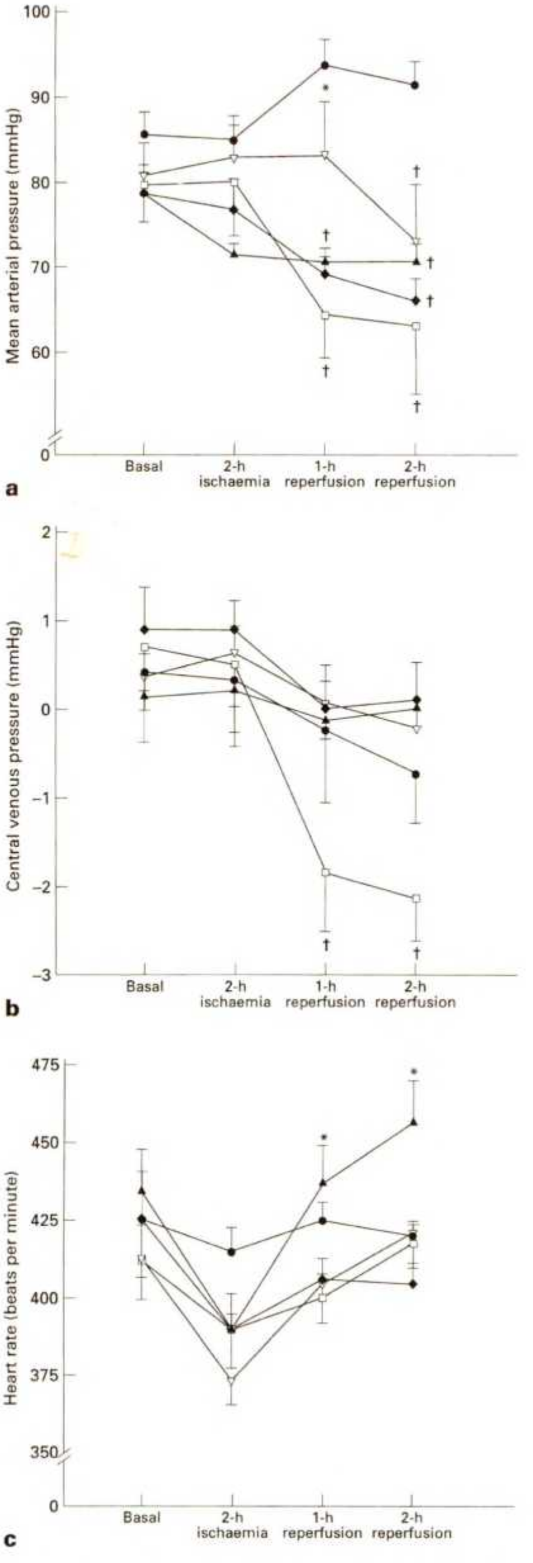

Fig. 1 Changes of **a** mean arterial pressure, **b** central venous pressure and **c** heart rate during ischaemia for 2 h and reperfusion for 2 h of the rat pancreas. Fifteen minutes before the end of ischaemia ▽, $18\,\mu g\,kg^{-1}\,h^{-1}$ CP-0597, ▲, $13\,\mu g\,kg^{-1}$ HOE-140 or ◆, $1{\cdot}5\,ml\,h^{-1}$ phosphate buffer were injected intravenously. ●, Sham-operated animals; □, ischaemia for 2 h without antagonists. Values are means; vertical bars represent s.e.m. $^*P < 0{\cdot}05$ *versus* 2-h ischaemia; $^\dagger P < 0{\cdot}05$ *versus* control ($n = 7$ in each group), Dunnett's method

method (normal distribution), or Friedman analysis of variance of ranks and Dunnett's method (non-normal distribution) were used to test differences between the groups. Differences were considered significant for $P < 0{\cdot}05$.

Results

The basal values of mean arterial pressure, CVP and heart rate and the systemic haematocrit and pancreas amylase concentration showed no significant differences between the five groups. Fewer than 10 per cent of animals were lost because of surgical faults. No animal died from acute pancreatitis after finishing the surgical procedure.

Macrohaemodynamics

Ischaemia of 2 h was associated with a significant fall in mean arterial pressure and CVP during reperfusion when compared with control animals. Heart rate showed a transient decrease during ischaemia but recovered completely at the end of the experiment. Animals given HOE-140 exhibited a slight decrease in arterial pressure at the end of ischaemia and a constant arterial pressure during reperfusion. In contrast, the mean arterial pressure of the animals who received CP-0597 was constant from the beginning of the experiment until 1 h of reperfusion, with a significant decrease at the end of the experiment. Neither antagonist had an effect on CVP, but heart rate increased significantly during reperfusion in the group treated with HOE-140. Animals treated with phosphate buffer showed no differences in mean arterial pressure and heart rate compared with the ischaemia group throughout the experiment, but CVP remained almost unchanged (*Figs 1a–c*).

Blood analysis

No significant changes were observed for haematocrit values during the entire experiment in control animals. Haematocrit increased significantly in the ischaemia group during reperfusion, but increased only slightly in the buffer group. The animals that were given CP-0597 showed an identical increase, to a value that was significantly different from the baseline value after reperfusion of 2 h. In contrast, the haematocrit did not increase during the entire experiment after administration of the antagonist HOE-140 (*Table 1*).

Serum pancreatic amylase concentration remained unchanged in the sham group, whereas the concentration was significantly increased in all other groups after reperfusion with no significant differences between these groups (*Table 1*).

Microhaemodynamics

FCD after ischaemia decreased during reperfusion; only 35 per cent of the capillaries perfused initially were reperfused 2 h after ischaemia and reperfusion for 2 h (FCD 30-min reperfusion control group: 408(9) cm^{-1}; 2-h reperfusion ischaemia group: 141(28) cm^{-1}). Similar values were obtained in the group that received phosphate buffer during reperfusion (FCD 2-h reperfusion: 166(11) cm^{-1}). Both bradykinin antagonists partially prevented non-perfusion of capillaries; 80 per cent more capillaries revealed red cell flow after reperfusion of 2 h when compared with the ischaemia group (FCD HOE-140: 260(6) cm^{-1}; CP-0597: 247(13) cm^{-1}). Decrease of FCD was associated with an increase in the index of capillary heterogeneity. In the ischaemia and phosphate buffer groups this index increased markedly as compared with the control group during reperfusion, which indicates a disturbance of the distribution of microvascular blood flow. The index of heterogeneity remained at a low level in both antagonist groups during the entire reperfusion period and this level was even lower in the group treated with HOE-140 (*Figs 2a, b*).

Analysis of leucocyte–endothelium interaction in control animals revealed that only a few leucocytes firmly adhered to the endothelium after 30 min of reperfusion (104(31) mm^{-2}) with a slight increase at the end of the experiment (820(52) mm^{-2}). The impairment of capillary perfusion in the ischaemia and phosphate buffer groups was accompanied by a significantly raised number of adherent leucocytes at 30 min of reperfusion followed by a significant increase throughout the reperfusion period (ischaemia group, 2-h reperfusion: 1969(86) mm^{-2}). In contrast to these results, the number of adherent leucocytes in the group given HOE-140 was similar to the number in the control group during the entire experiment (101(39) mm^{-2}) and increased only slightly throughout the reperfusion period (630(61) mm^{-2}). The bradykinin antagonist CP-0597 also produced significantly lower numbers of adherent leucocytes during the observation time compared with the control group (*Fig. 3*). Examination of the fraction of rolling leucocytes revealed no significant differences between the groups, with values not higher than 20 per cent during reperfusion. The numbers of adherent leucocytes were inversely proportional to the numbers of rolling leucocytes in all groups.

Discussion

Using an ischaemia–reperfusion model of the rat pancreas, which permits intravital microscopy of the

Table 1 Mean(s.e.m.) changes of arterial haematocrit and serum α-amylase concentration, basal and after reperfusion of 2 h, of the rat pancreas

	Haematocrit		Amylase	
Treatment group	Basal	2-h reperfusion	Basal	2-h reperfusion
Sham	41(0·6)	40(0·4)	2048(151)	1857(99)
2-h ischaemia	42(0·5)	46(1·3)†	2434(285)	2967(290)†
2-h ischaemia + CP-0597	40(0·6)	45(1·1)†	2177(370)	3158(453)†
2-h ischaemia + buffer	38(0·5)	41(0·4)*	2874(294)	3492(107)†
2-h ischaemia + HOE-140	39(0·3)	39(0·2)*	2103(214)	2941(401)†

*$P < 0{\cdot}05$ *versus* 2-h ischaemia, Friedman analysis; †$P < 0{\cdot}05$ *versus* basal, Dunnett's method

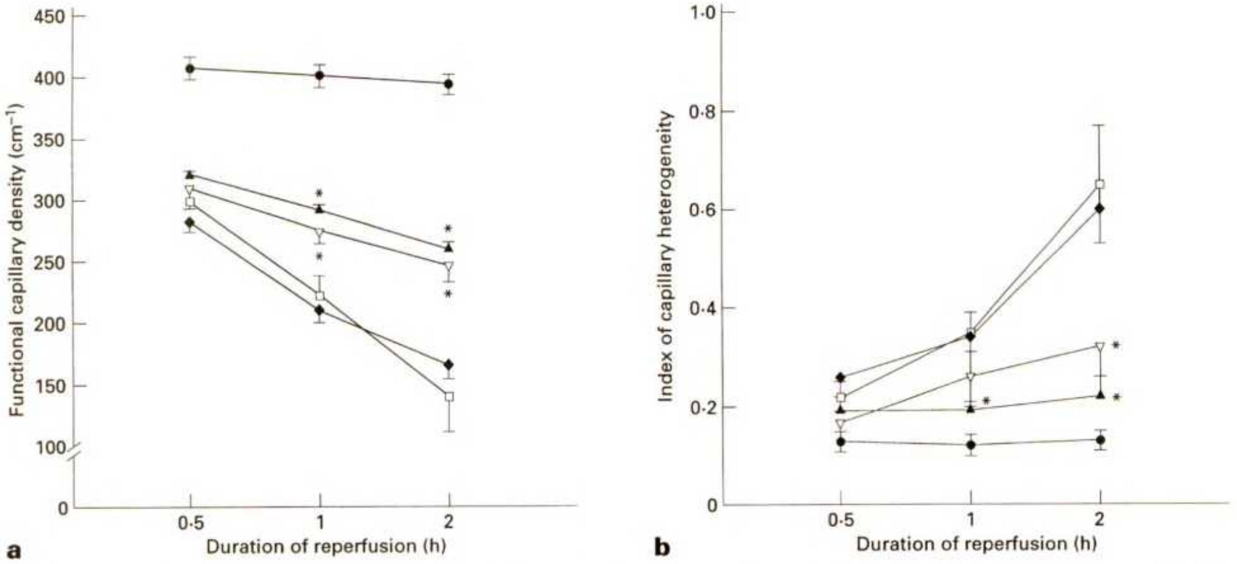

Fig. 2 Changes of **a** functional capillary density and **b** index of capillary heterogeneity after ischaemia of 2 h and during reperfusion of 2 h of the rat pancreas. Values are means; vertical bars represent s.e.m. ●, Sham-operated animals; □, 2-h ischaemia, ▽ 2-h ischaemia + CP-0597; ◆, 2-h ischaemia + buffer; ▲, 2-h ischaemia + HOE-140. *$P < 0{\cdot}05$ *versus* 2-h ischaemia, Dunnett's method

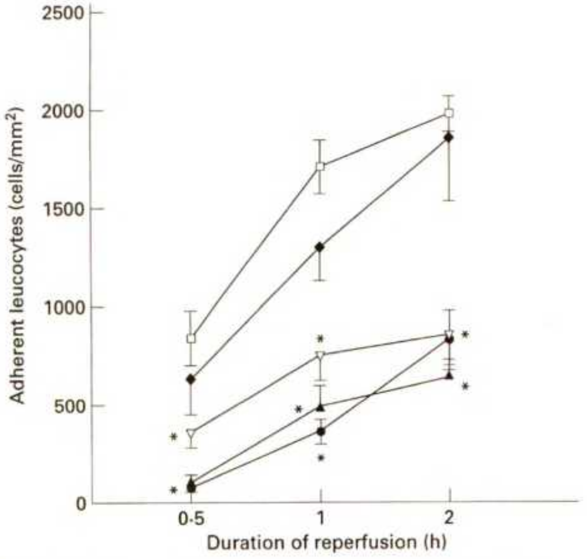

Fig. 3 Leucocyte–endothelium interaction in postcapillary venules; number of adherent leucocytes (stickers) per endothelial surface area (mm^2). Values are mean; vertical bars represent s.e.m. ●, Sham-operated animals; □, 2-h ischaemia, ▽ 2-h ischaemia + CP-0597; ◆, 2-h ischaemia + buffer; ▲, 2-h ischaemia + HOE-140. *$P < 0{\cdot}05$ *versus* 2-h ischaemia, Dunnett's method

microcirculation in the pancreas, the microcirculatory changes were investigated after pancreatic ischaemia–reperfusion of two different bradykinin antagonists. HOE-140 and CP-0597 effectively attenuated postischaemic microvascular perfusion failure; 80 per cent more capillaries were found perfused in the treatment groups after reperfusion of 2 h compared with the group that underwent ischaemia without antagonists (*Figs 4a–c*). The increase in heterogeneity of capillary perfusion, indicating disturbed distribution of microvascular perfusion, was less marked in the treatment groups. In addition, postischaemic leucocyte–endothelium interaction in postcapillary venules was significantly reduced in CP-0597-treated animals (*Figs 5a–c*). In HOE-140-treated animals this interaction was almost completely abolished and the numbers of adherent leucocytes were similar to those of control animals. This effect of HOE-140 on the leucocyte–endothelium interaction was associated with a constant arterial haematocrit during reperfusion, indicating preservation of the integrity of the endothelial wall in contrast to the ischaemia group without treatment. In the ischaemia group and in the two antagonist-treated groups a significant increase was observed in pancreatic amylase concentration compared with the control group, but no differences were seen between the ischaemia and antagonist groups, in agreement with the results of other authors[21].

The vasoactive polypeptide bradykinin is known to be involved in the pathogenesis of the characteristic manifestations and pathophysiological features of acute haemorrhagic pancreatitis[22] such as vasodilatation, increased capillary permeability, hypotension and polymorphonuclear leucocyte accumulation. The role of the kallikrein–kinin system in the pathogenesis of acute pancreatitis has been discussed extensively[3,4,23–27]. Kinin, a vasoactive substance, is believed to be involved in pancreatic malperfusion, which is a characteristic phenomenon and a crucial factor in the development of acute pancreatitis[4]. Furthermore, high concentrations of bradykinin have been observed during the course of experimental pancreatitis; the hormone is largely produced within the pancreas itself, acting and being destroyed locally[25].

Conversely, the pancreas is highly susceptible to ischaemic injury[28] and the resulting impairment of microvascular perfusion may play an important role in the initiation and aggravation of acute pancreatitis[8,11,13]. Ischaemia–reperfusion injury of the pancreas is characterized by capillary perfusion failure[18], activation of circulating leucocytes[29] and loss of endothelial integrity with an accompanying increase of microvascular permeability[19]. Postischaemic leucocyte–endothelium interaction is heralded by accumulation and adherence of leucocytes in microvessels as a result of oxygen-radical

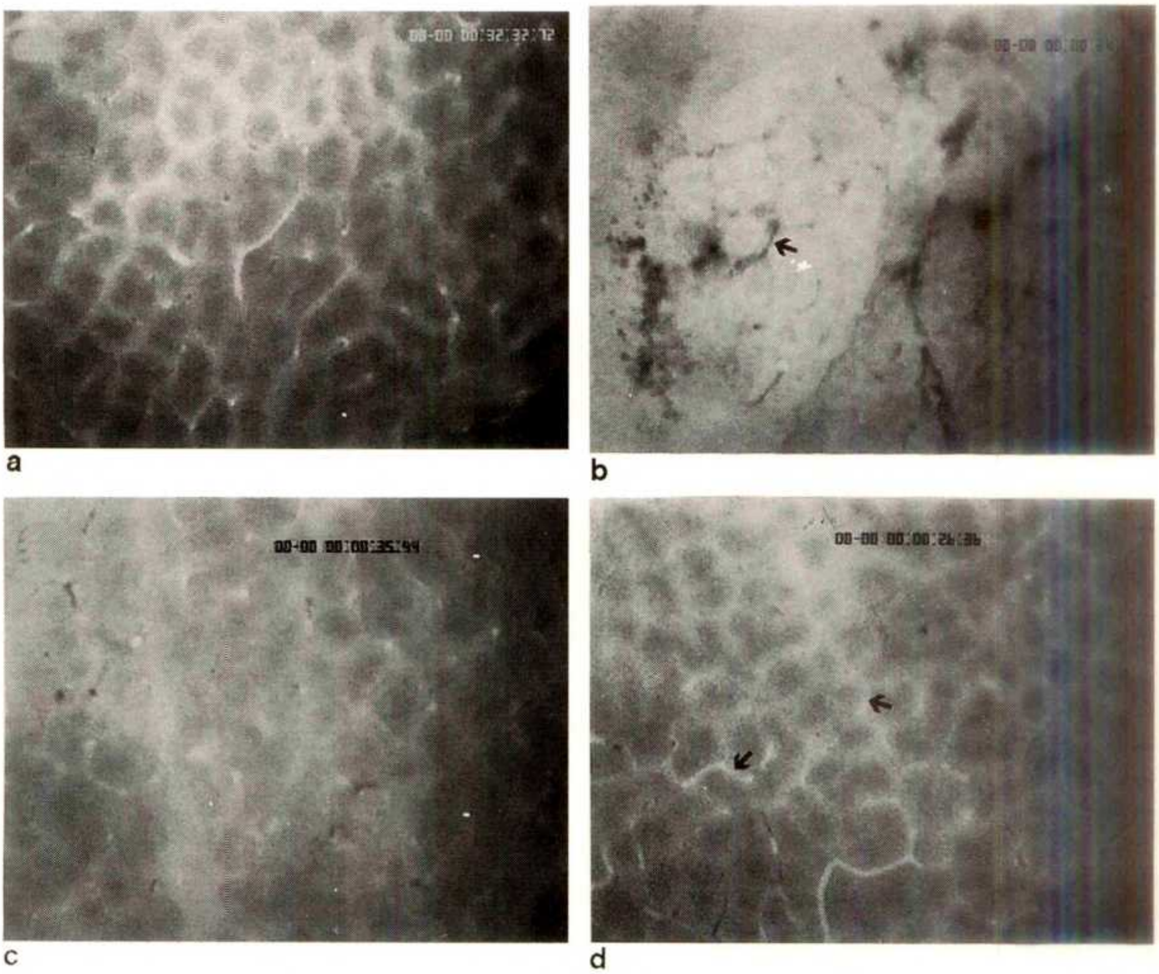

Fig. 4 Intravital microscopic images of pancreas capillary perfusion (contrast enhancement with 0·15 ml 0·75 per cent) FITC–HES hydroxyethylstarch labelled with fluorescein isothiocyanate (intravenous, ×25). **a** Control: homogeneous perfusion of capillary network. **b** Ischaemia for 2 h: identical networks, inversion of contrast caused by extravasation of FITC–HES resulting in staining of tissue (white areas). Only a few capillaries are perfused (arrow). **c** Ischaemia for 2 h and infusion of CP-0597. **d** Ischaemia for 2 h and injection of HOE-140: 80 per cent more perfused capillaries (arrows) compared with **b**

mediated adhesive interactions between leucocytes and endothelial cells[30]. This interaction is located primarily in the postcapillary venules and is controlled by upregulation and expression of adhesion molecules on leucocytes and endothelial cells[19]. Leucocyte adhesion to and migration across the endothelial wall of postcapillary venules are associated with impairment of microvessel permeability and macromolecular leakage[31,32].

These cardinal features of ischaemia–reperfusion injury – capillary perfusion failure and enhanced leucocyte–endothelium interaction – are influenced by kinins which are able to stimulate the release of cytokines and other mediators[33–35]. Bradykinin is a key enzyme in the activation of phospholipase A_2 and generates prostaglandins and leukotrienes[36], which are involved in ischaemia–reperfusion injury[31], promoting arteriolar constriction, macromolecular leakage and leucocyte adhesion to and migration across the endothelial wall of postcapillary venules[31,32]. This triad of effects induced by leukotrienes bears a close resemblance to the early events in acute inflammatory reactions as seen also in acute pancreatitis[32]. Inhibition of endogenous leukotriene biosynthesis has been shown entirely to prevent microcirculatory changes of ischaemia–reperfusion in striated muscles[31]. In addition, it has been discovered recently that neutrophils have receptors that bind and activate kininogens[37,38]. Kallikrein can form kinins, which by opening gap junctions between endothelial cells may promote local diapedesis of neutrophils and the extravasation of plasma constituents[37,39,40]. The two bradykinin antagonists tested here have different effects on the leucocyte–endothelium interaction. The explanation could be the short half-life of CP-0597, but there may also be different affinity to the bradykinin receptor. This would explain the increase of arterial haematocrit in the animals given CP-0597, indicating loss of endothelial integrity and plasma leakage in contrast to those given HOE-140.

In conclusion, ischaemia–reperfusion-induced microvascular perfusion failure, heterogeneity of capillary perfusion and enhanced leucocyte adherence in postcapillary venules can be effectively inhibited by injection of HOE-140 or infusion of CP-0597. These results suggest that bradykinin is involved in

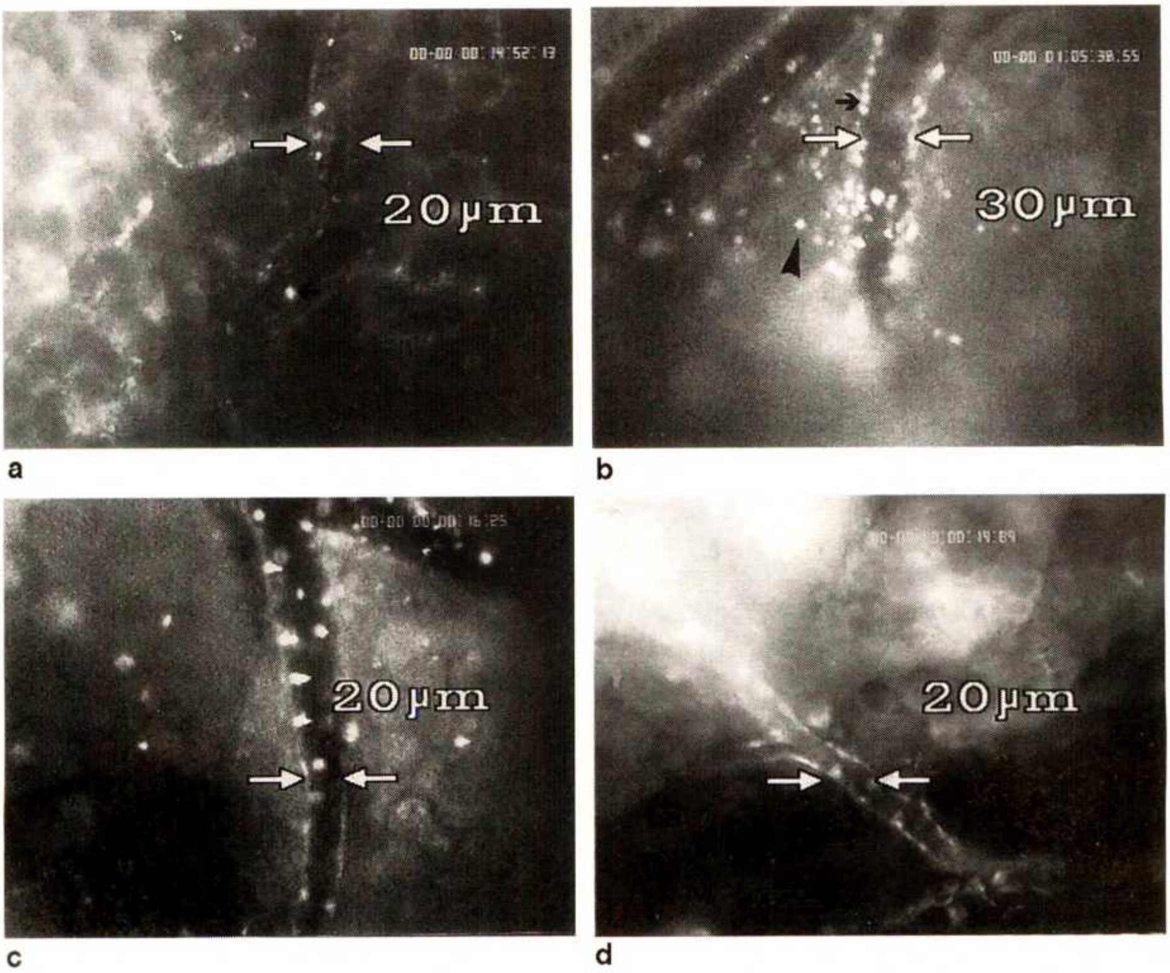

Fig. 5 Intravital microscopic images of pancreas leucocyte–endothelium interaction (*in vivo* staining by 0·2 per cent Rhodamine 6G intravenous). **a** Control: in the centre one leucocyte (black arrows). **b** Ischaemia for 2 h: adherent leucocytes (black arrows), migrated leucocytes in the surrounding tissue (black arrow head). **c** Ischaemia for 2 h and infusion of CP-0597: adherence and migration of leucocytes is less marked than in animals after 2 h of ischaemia. **d** Ischaemia for 2 h and injection of HOE-140: only a few adherent leucocytes, absence of migrated leucocytes

postischaemic reperfusion injury of the pancreas and that treatment with bradykinin antagonists can limit the microcirculatory dysfunction and the progression of postischaemic pancreatitis.

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Anabolic and cardiovascular effects of recombinant human growth hormone in surgical patients with sepsis

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The clinical and metabolic effects of 7 days of recombinant human growth hormone (rhGH) and total parenteral nutrition (TPN) in surgical patients with sepsis were determined in a randomized controlled trial. In patients with a mean(s.e.m.) pretreatment rate of net protein catabolism (NPC) of 1·5 g per kg per day or less rhGH treatment decreased NPC from 0·93(0·14) to −0·20(0·24) g per kg per day ($n=5$; $P<0·0005$) and rendered these patients anabolic. TPN alone decreased NPC from 1·12(0·11) to 0·61(0·11) g per kg per day ($n=5$; $P<0·001$). In patients with an initial NPC of more than 1·5 g per kg per day rhGH treatment decreased NPC from 2·72(0·12) to 1·08(0·24) g per kg per day ($n=5$; $P<0·001$) while TPN alone decreased it from 2·41(0·32) to 1·28(0·28) g per kg per day ($n=5$; $P<0·005$). Use of rhGH was not associated with any adverse effects or improvement in clinical course but did decrease the mean systolic and diastolic pressures during the study period. Thus rhGH is a useful anabolic agent and may have a role in the haemodynamic management of the catabolic patient with sepsis.

In surgical patients severe sepsis results in accelerated loss of tissue protein, impairment of organ function, increased operative morbidity and prolonged hospital stay and convalescence[1–3]. Unfortunately nutritional support alone does not prevent this sequence of events and it is now clear that total parenteral nutrition (TPN) is unable to reverse protein loss in surgical patients with sepsis[4] or improve in-hospital morbidity or stay[5]. Consequently the use of TPN combined with adjuvant recombinant human growth hormone (rhGH) is being examined to determine whether the anabolic actions of rhGH can diminish protein loss and improve the clinical course of catabolic patients.

While a number of investigations has demonstrated that growth hormone can favourably influence protein metabolism in catabolic patients no investigation has yet documented an improved clinical course or outcome attributable to rhGH administration, although Jiang *et al.*[16] and Vara-Thorbeck and colleagues[7] have documented improvements in voluntary muscle function and immune function, respectively, in stable postoperative patients. However, if rhGH is to have a clinical role as an anabolic agent it is likely to be in the management of severely stressed, catabolic patients who are haemodynamically stable, but who require vigorous nutritional support. Ideally a course of rhGH treatment given over a defined period in addition to nutritional support should decrease protein loss, enhance physiological function and improve clinical outcome without causing adverse effects. The aim of this investigation was to define the clinical and metabolic effects of 7 days of rhGH treatment in addition to TPN in surgical patients with protein catabolism caused by severe sepsis.

Patients and methods

This study was a randomized, double-blind, placebo-controlled trial performed in patients presenting with sepsis to the Department of Surgery at Auckland Hospital. The study was approved by the ethics committee at Auckland Hospital and written informed consent was taken before enrolment in the study from either the patient or their nominated next of kin. A diagnosis of sepsis was based on the presence of at least three of the following (one from each of 1, 2 and 3), using a modification of Dunn's criteria[8]:

1. Core (rectal or oral) temperature of more than 38°C or less than 36°C.
2. Leucocytosis with a white cell count greater than 15×10^9 per l, leucopenia with a white cell count less than 5×10^9 per l or thrombocytopenia with a total platelet count below 100×10^9 per l.
3. A septic focus demonstrated either surgically or by radiological investigation, or one or more positive blood cultures.

Patients with sepsis were not included in the trial if immunocompromised by either human immunodeficiency virus infection or the presence of renal failure. Patients with insulin-dependent diabetes mellitus or malignancy were also excluded.

Patients

A summary of the details of the 20 patients included in the investigation and their sepsis scores at enrolment is presented in *Table 1.*

Experimental protocol

The study period was 10 days although the clinical course of the patients was followed until discharge or death, and the total duration of parenteral nutrition and hospital stay was recorded. Following enrolment the patients were randomized to receive either 7 days of TPN plus twice daily subcutaneous injections of a placebo or TPN plus twice daily subcutaneous injections of rhGH (Genotropin, donated by Kabi Pharmacia Peptide Hormones, Stockholm, Sweden) at a total daily dose of 0·3 units per kg body-weight. Placebo or growth hormone was administered at 08.00 and 20.00 hours daily.

Immediately before the start of TPN (baseline period) and after 7 days of TPN the rate of net protein catabolism (NPC) was determined using a primed constant infusion of [^{15}N] urea[9,10]. A

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Table 1 Patient demographics, diagnosis, sepsis score at enrolment and clinical outcome

Patient no.	Age	Sex	Diagnosis	Sepsis score	Procedure	Outcome
Recombinant human growth hormone treatment						
1	78	F	Peritonitis	14	Small bowel resection	Died
2	54	M	Pancreatic abscess	7	Splenectomy	Survived
3	79	F	Pelvic abscess	8	Laparotomy	Survived
4	60	M	Subphrenic abscess	17	Splenectomy	Survived
5	58	F	Cholangitis	6	Chole + CBD	Survived
6	61	F	Acute colitis	17	Colectomy	Survived
7	56	M	Pancreatitis	11	Laparotomy	Survived
8	76	M	Pancreatitis	13	Nil	Survived
9	71	F	Peritonitis	12	Colectomy	Survived
10	50	M	Peritonitis	14	Colectomy	Survived
Placebo treatment						
1	79	F	Pancreatitis	4	Nil	Survived
2	57	M	Pancreatitis	13	Necrosectomy	Survived
3	82	F	Peritonitis	14	Colectomy	Survived
4	62	M	Peritonitis	18	Laparotomy	Survived
5	54	M	Pancreatitis	12	Nil	Survived
6	85	M	Peritonitis	12	Chole + CBD	Survived
7	54	F	Pancreatic abscess	12	Radiology*	Survived
8	34	M	Pelvic abscess	10	Laparotomy	Survived
9	52	F	Pelvic abscess	12	Small bowel resection	Survived
10	58	F	Mediastinitis	14	Thoractomy	Survived

*Percutaneous radiologically guided drain placement; Chole + CBD, open cholecystectomy and exploration of the common bile duct

blood sample was also taken, and the plasma separated before being rapidly frozen in liquid nitrogen for measurement of insulin-like growth factor I (IGF-I), growth hormone, insulin and cortisol concentrations.

At 08.00 hours each day the sepsis score[11], Kehlet score[12], and Karnovsky performance index[13] were measured. The daily pulse rate, blood pressure, oral temperature and respiratory rate were also recorded at 08.00 hours. At the same time blood was collected for the determination of haematocrit, haemoglobin, platelet and white cell concentration. Plasma urea and electrolyte concentrations and liver function were determined daily.

Concomitant treatment

Parenteral recombinant human insulin (Humulin R; Eli Lilly, Indianapolis, Indiana, USA) was given to any patient following two consecutive blood glucose measurements of more than 10 mmol/l. Blood glucose determinations were made every 4 h following the start of TPN.

All patients received broad spectrum intravenous antibiotic therapy with either an intravenous cephalosporin (cefuroxime) and the antianaerobic agent, metronidazole, or an intravenous aminoglycoside (gentamicin), penicillin (amoxycillin) and metronidazole for at least 7 days. In addition all patients received oral nystatin 100 000 units four times daily and intravenous ranitidine 150 mg daily. Analgesia was provided with paracetamol 1 g administered rectally every 4 h and papaveretum 0·1 mg/kg administered intramuscularly up to every 4 h according to patient demand.

Total parenteral nutrition

Patients in both treatment groups were given an identical TPN prescription which was administered as a 24-h continuous infusion through a central venous line. All patients received between 2000 and 2500 kcal (8·4 and 10·5 MJ) per day as non-protein calories. The energy requirement of individual patients was determined using an estimation of 40 kcal (167 kJ) per kg per day, of which 50 per cent of calories were provided as fat (Intralipid 20; Kabi Pharmacia, Stockholm, Sweden) and 50 per cent as glucose[14]. The nitrogen intake was provided as a balanced amino acid solution (Synthamin 17; Travenol Laboratories, Toongabbie, New South Wales, Australia) at 1·5 g protein per kg per day[4,14] together with intravenous electrolytes adjusted according to daily plasma electrolyte determinations. Vitamins and trace elements were provided by daily administration of one vial of MVI-12 (Rhone-Poulenc Rorer, Montreal, Canada), vitamin K 20 mg intramuscularly per week and vitamin B_{12} 1000 μg intramuscularly every month. TPN was discontinued when the patient was able to maintain an oral intake of 1000 (4·2 MJ) kcal per day measured by an independent dietitian blinded to treatment.

Hormone assays

The plasma concentrations of growth hormone and insulin were determined using double antibody radioimmunoassay.

Plasma cortisol was measured using an Amerlex radio-immunoassay kit (Amersham International, Amersham, UK).

Plasma IGF-I was determined with a double antibody radioimmunoassay using a rabbit antiserum to recombinant human met-insulin-like growth factor 1 at a final titre of 1:250 000 following extraction of plasma binding proteins using the acid–ethanol cryoprecipitation technique[15]. Excess IGF-II was added to neutralize the effect of IGF-I binding proteins. This assay has been validated extensively for human plasma IGF-I determination[16].

Statistical analysis

The data obtained from within the patient groups were compared using a Student's paired *t* test. Plots of the cumulative distribution of values for NPC and plasma hormone concentrations confirmed these data to be normally distributed. Data from patients who received TPN and placebo were compared with data from those given TPN and rhGH by analysis of variance. Where appropriate, multiple measures of significance were made within groups using a repeated measures analysis of variance. All data are presented as mean(s.e.m.).

Results

Demographics

There was no significant difference between the groups given rhGH and placebo in terms of age (mean(s.e.m.)

71·2(2·9) *versus* 72·9(2·6) years respectively), recalled body-weight when well (mean(s.e.m.) 78·4(5·2) *versus* 72·5(6·4) kg), or body-weight at the start of the study (mean(s.e.m.) 70·7(5·1) *versus* 64·7(5·9) kg). All patients were clinically malnourished at enrolment. Patients treated with rhGH had lost a mean 10 per cent of their weight when well (mean baseline plasma albumin 26 g/l) and those receiving placebo a mean 15 per cent of normal weight (mean baseline plasma albumin 27 g/l).

Patients treated with rhGH had been hospitalized for a mean(s.e.m.) 12·4(2·9) days and had sepsis for a mean(s.e.m.) 11·8(3·3) days before enrolment. Those given placebo had been suffering from sepsis for a mean(s.e.m.) 10·8(2·2) days before enrolment and had been hospitalized for longer than patients receiving rhGH (28·0(13·1) days) although this did not reach statistical significance ($P < 0\cdot9$).

Protein metabolism

At enrolment the mean(s.e.m.) rate of NPC of 1·77(0·27) g per kg per day in the placebo group was similar to the rate of 1·82(0·31) g per kg per day in rhGH-treated patients. TPN alone for 7 days decreased the mean(s.e.m.) rate of NPC to 0·95(0·2) g per kg per day ($P < 0\cdot001$), while 7 days of TPN and rhGH decreased the rate of NPC to 0·44(0·27) g per kg per day ($P < 0\cdot0001$). Treatment with rhGH and TPN for 7 days resulted in a greater ($P < 0\cdot05$) mean percentage decrease in NPC than TPN alone (mean(s.e.m.) 92·8(16·8) *versus* 45·4(7·5) per cent).

The differences in the anabolic response to rhGH therapy were more apparent when the patients were stratified on the basis of their baseline rate of NPC. In five patients each treated with rhGH or placebo the initial NPC was less than or equal to 1·5 g protein per kg per day (moderately catabolic patients) and in five patients in each group the initial NPC exceeded this figure (severely catabolic patients). In the moderately catabolic patients, treatment with rhGH and TPN decreased the mean(s.e.m.) initial rate of NPC from 0·93(0·14) to −0·20(0·24) g per kg per day ($P < 0\cdot0005$; *Fig. 1*) and rendered these patients anabolic. This was a greater ($P < 0\cdot05$) improvement in NPC than treatment with TPN alone which resulted in a mean(s.e.m.) decrease in NPC from 1·12(0·11) to 0·61(0·11) g per kg per day ($P < 0\cdot001$).

Treatment with rhGH and TPN in severely catabolic patients decreased the rate of NPC from 2·72(0·12) to 1·08(0·24) g per kg per day ($P < 0\cdot001$) while administration of TPN alone produced a decrease in NPC from 2·41(0·32) to 1·28(0·28) g per kg per day ($P < 0\cdot005$; *Fig. 1*).

Fluid balance and haemodynamic parameters

There was no difference in the total daily fluid balance between the two groups at baseline (mean(s.e.m.) + 1410(360) *versus* + 1220(250) ml respectively) or after 7 days of treatment (+ 1180(100) *versus* + 1270(170) ml).

The haemodynamic data for the two patient groups are summarized in *Fig. 2*. Pulse rate and pulse pressure remained comparable between the two treatment groups throughout the study period in both moderately and severely catabolic patients. However, the mean arterial blood pressure was lower in patients treated with rhGH by day 5. This was due to a significant fall in diastolic and systolic blood pressure in the patients treated with growth hormone on days 5–7 inclusive (*Fig. 2*).

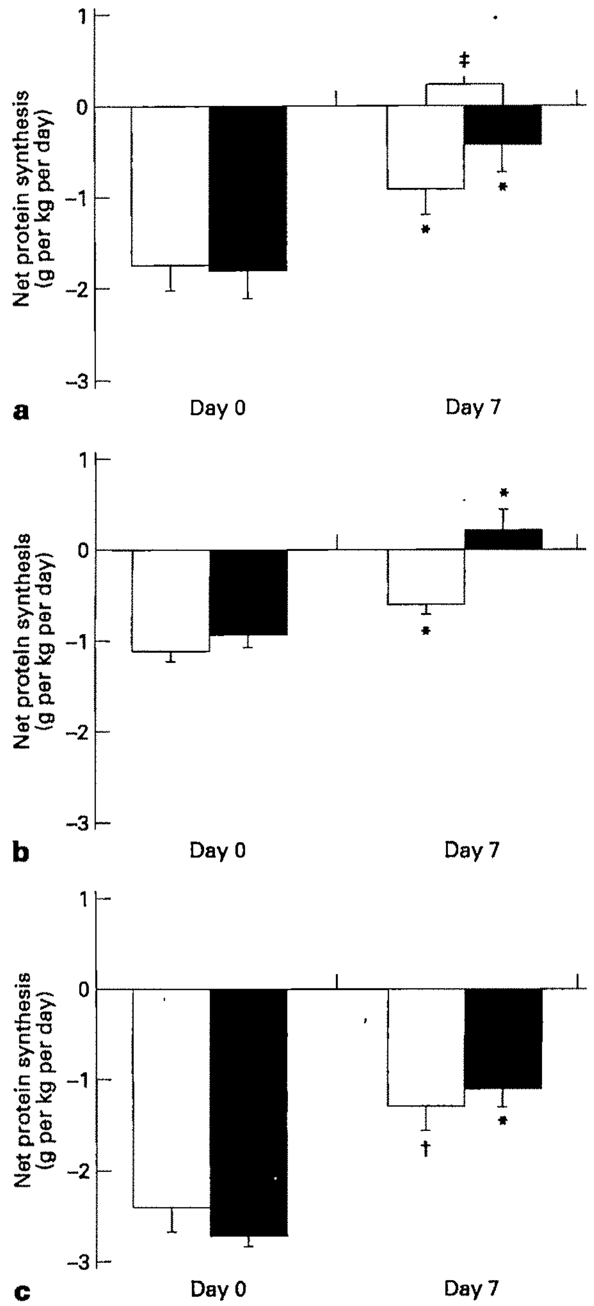

Fig. 1 Net protein catabolism at baseline and on day 7 in patients receiving total parenteral nutrition with placebo (□) or human growth hormone (■) a for all patients ($n = 10$ in each group), b for moderately catabolic patients ($n = 5$ in each group) and c for severely catabolic patients ($n = 5$ in each group). Values are mean(s.e.m.). *$P < 0\cdot001$, †$P < 0\cdot01$ *versus* baseline value (Student's t test), ‡$P < 0\cdot06$ (analysis of variance)

Plasma hormone concentrations

There was no difference in plasma IGF-I, growth hormone, insulin or cortisol concentrations between patients treated with rhGH or placebo at baseline (*Tables 2* and *3*). However, 7 days of treatment with rhGH increased mean circulating insulin, growth hormone and IGF-I levels while plasma cortisol concentrations remained unchanged in both moderately and severely catabolic patients.

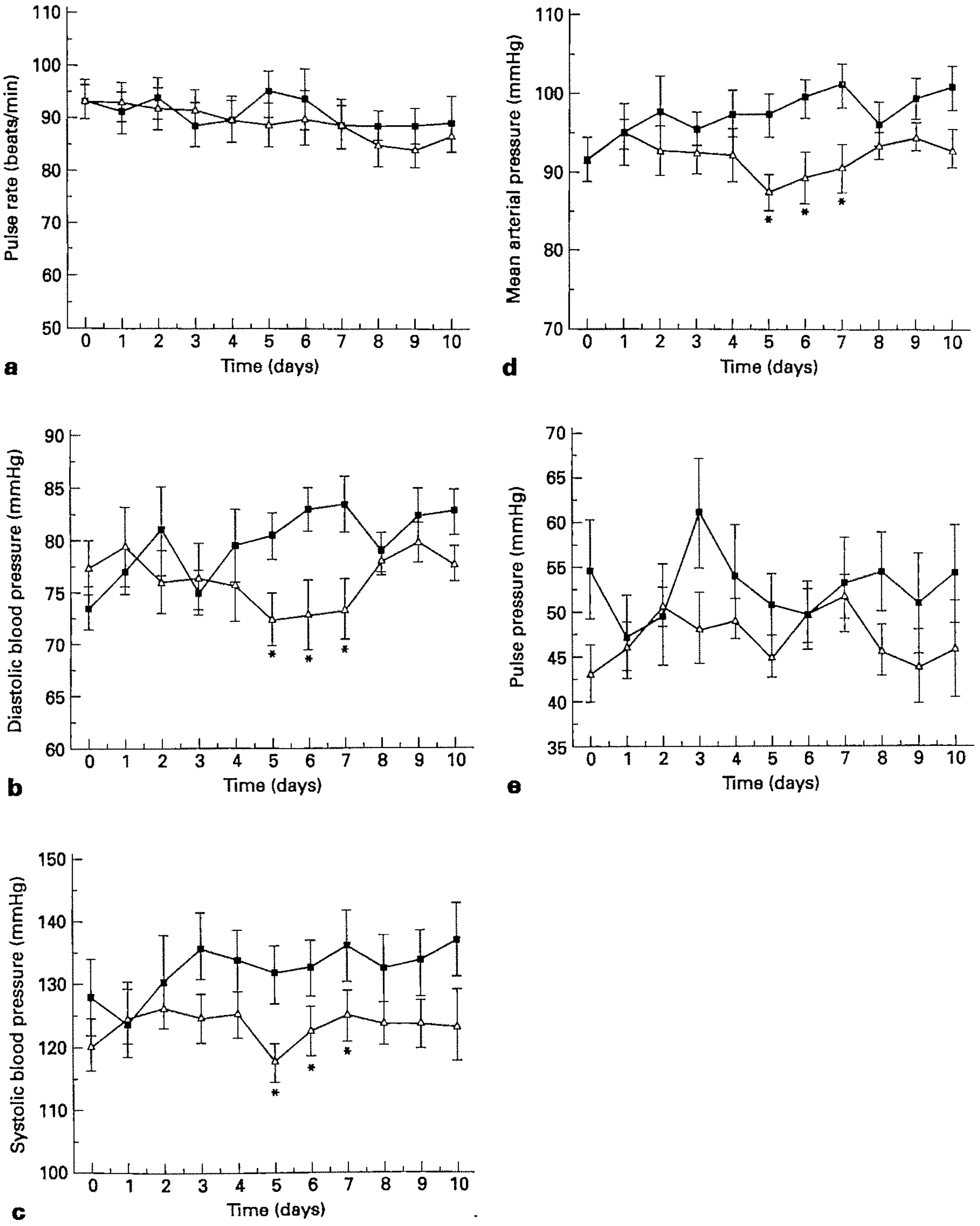

Fig. 2 Mean(s.e.m.) values at 08.00 hours daily for **a** pulse rate, **b** diastolic pressure, **c** systolic pressure, **d** mean arterial pressure and **e** pulse pressure in patients treated with growth hormone (△) or placebo (■). $^{*}P < 0{\cdot}05$ *versus* placebo-treated patients (analysis of variance)

Clinical progress

There was no significant difference between the mean sepsis scores of the two treatment groups either at baseline (mean(s.e.m.) 12·1(1·1) in rhGH-treated patients and 12·2(1·2) in placebo-treated patients) or on any day of the study period. The sepsis score became significantly different from baseline in both groups on day 1 and continued to improve in both throughout the 10-day study period (*Table 4*). The Kehlet score and Karnovsky performance index did not differ significantly between the two groups at any stage (*Table 4*).

Plasma glucose concentration and insulin requirement

The mean(s.e.m.) baseline plasma glucose concentration was 7·0(0·3) mmol/l and 6·3(1·1) mmol/l in patients treated with rhGH and placebo respectively. Five patients from

Table 2 Plasma hormone concentrations in moderately catabolic patients (initial net protein catabolism 1·5 g per kg per day or less) treated with growth hormone or placebo at baseline and on day 7

Hormone	Baseline	Day 7	P*
HGH (μg/l)			
rhGH	1·1(0·2)	16·0(3·5)	<0·001
Placebo	2·5(1·1)	1·9(0·4)	n.s.
IGF-I (ng/ml)			
rhGH	58·0(14·9)	328·7(56·0)	<0·0001
Placebo	84·5(16·4)	144·3(22·1)	<0·003
Insulin (milliunits/l)			
rhGH	19·2(4·8)	98·3(27·2)	<0·005
Placebo	26·4(11·5)	60·1(20·8)	<0·02
Cortisol (mmol/l)			
rhGH	696·6(98·6)	465·6(47·87)	n.s.
Placebo	433·4(72·9)	515·4(122·4)	n.s.

Values are mean(s.e.m.). HGH, human growth hormone; rhGH, recombinant human growth hormone; IGF-I, insulin-like growth factor I; n.s., not significant. *Student's *t* test

Table 3 Plasma hormone concentrations in severely catabolic patients (initial net protein catabolism above 1·5 g per kg per day) treated with growth hormone or placebo at baseline and on day 7

Hormone	Baseline	Day 7	P*
HGH (μg/l)			
rhGH	1·0(0·3)	14·9(5·5)	<0·005
Placebo	1·5(0·3)	1·5(0·5)	n.s.
IGF-I (ng/ml)			
rhGH	49·0(5·1)	361·0(68·6)	<0·001
Placebo	80·7(20·1)	132·2(36·1)	<0·05
Insulin (milliunits/l)			
rhGH	13·5(1·6)	186·9(58·4)	<0·001
Placebo	17·6(6·2)	75·8(28·7)	<0·02
Cortisol (mmol/l)			
rhGH	971·9(411·4)	627·5(120·5)	n.s.
Placebo	463·5(38·1)	459·5(47·3)	n.s.

Values are mean(s.e.m.). HGH, human growth hormone; rhGH, recombinant human growth hormone; IGF-I, insulin-like growth factor I; n.s., not significant. *Student's *t* test

Table 4 Sepsis, Karnovsky and Kehlet scores in patients treated with hormone and placebo

	Day 1	Day 7
Recombinant human growth hormone		
Sepsis score	10·6(1·2)	8·7(1·7)
Karnovsky score	23·0(3·0)	29·0(5·7)
Kehlet score	9·8(0·1)	8·2(0·5)
Placebo treatment		
Sepsis score	10·2(1·7)	7·7(1·8)
Karnovsky score	21·0(4·1)	24·0(5·8)
Kehlet score	10·0(0·1)	8·9(0·5)

Values are mean(s.e.m.)

the rhGH group, two of whom had pancreatitis, required insulin at a mean daily dose of 28 units instituted between days 1 and 5 of the trial to maintain blood glucose concentration below 10 mmol/l. No patient required insulin beyond day 10. In the placebo group two patients required a mean daily insulin dose of 32 units to maintain blood glucose concentration below 10 mmol/l beginning on day 1 of treatment, and ceasing on days 20 and 4.

Haematology and electrolytes

The haemoglobin concentration, platelet and leucocyte counts, plasma electrolytes and liver function did not differ between the groups at any time during the study.

Clinical outcome

There was one death in the rhGH group (patient 1) 65 days after admission (37 days after final dose of rhGH) from renal failure. Patients who received rhGH spent a mean(s.e.m.) 37·8(5·3) days in hospital and required 19·9(3·1) days of intravenous feeding. Those who received placebo injections spent a mean(s.e.m.) 53·4(11·1) days in hospital and required 15·5(2·1) days of TPN ($P < 0·2$ with respect to rhGH-treated patients). There were no differences in intensive care unit stay, duration of mechanical ventilation, or nosocomial infection rate between the treatment groups. Even when the clinical outcome was analysed in terms of moderate or severe protein catabolism at baseline there were no differences between the groups in either the total duration of hospital stay following treatment or the duration of parenteral feeding.

Discussion

This randomized controlled trial was undertaken to define the metabolic effects and clinical results of a short course of rhGH in addition to standard TPN in a group of catabolic surgical patients with sepsis. All patients completed the treatment and rhGH was well tolerated. The reported side-effects of growth hormone administration of pain and skin rash at the injection site[17] and fluid retention[7] did not occur in this study.

In this investigation 7 days of rhGH therapy resulted in significant protein conservation in the catabolic surgical patient. This has been reported previously in a non-randomized trial of surgical patients[18]. Other reports have described the protein sparing effects of rhGH in stable postoperative patients[19–21], and those with burns[22], cancer[23], chronic obstructive pulmonary disease[24], and renal failure[25]. However, the protein sparing effect of rhGH was most marked in the less catabolic patients and the initial degree of catabolism was an important determinant of the later anabolic response to rhGH. Patients with an initial rate of NPC of 1·5 g per kg per day or less were rendered anabolic by rhGH while those with an initial rate of NPC of more than 1·5 g per kg per day experienced a 60 per cent reduction in NPC but remained catabolic.

The mechanism underlying the lower responsiveness to rhGH in more catabolic patients is unclear. However, as many of the anabolic effects of growth hormone are attributable to IGF-I and since the increase in circulating IGF-I was similar in both moderately and severely catabolic patients, it seems that severely catabolic patients are resistant to the protein sparing action of IGF-I at a receptor or postreceptor level. Alternatively, severely catabolic patients may have altered IGF binding protein (IGFBP) kinetics leading to a decrease in the fraction of biologically active IGF-I available. Downregulation of the type 1 IGF-I receptor is known to occur in severely catabolic states particularly when associated with high levels of circulating IGF-I[26]. Downregulation of the type 1 receptor also occurs with increasing age[27]. Thissen and colleagues[28] have documented resistance to the anabolic actions of IGF-I in chronically protein-depleted rats receiving IGF-I in spite of high circulating IGF-I concentrations and adequate numbers of type 1 receptors. Consequently the elderly, protein-depleted patients in this investigation may have had a postreceptor defect leading to IGF-I inactivity or insufficient IGF-I receptors for full expression of the anabolic effects of circulating IGF-I.

Alterations in IGFBP concentrations are also known to occur in catabolic patients. Ross *et al.*[29] have shown that increased levels of IGFBP-I, which may inhibit the cellular actions of IGF-I, are present in the plasma of fasted catabolic intensive care patients. Similarly catabolic patients with acquired immunodeficiency syndrome have decreased circulating levels of IGFBP-3[26], which acts as a reservoir for IGF-I. Low levels of IGFBP-3 may lead to increased levels of free IGF-I, more rapid elimination and decreased biological activity. Low levels of IGFBP-3 are also associated with downregulation of the type 1 receptor[30].

It has been shown that the protein sparing effects of rhGH are optimal when associated with a relative hyperinsulinaemia and an enhanced amino acid supply[23,31]. The mechanism underlying this is probably insulin-mediated suppression of IGFBP-1 thereby freeing available IGF-I for binding with IGFBP-3. In the present study plasma insulin concentration increased with rhGH treatment in both moderately and severely catabolic patients although a diminution in protein sparing occurred when the initial rate of catabolism exceeded the parenteral protein dose (1·5 g per kg per day). This may indicate that insufficient substrate was provided to these patients and correspondingly parenteral hyperalimentation may have a role in the severely catabolic patient when combined with rhGH therapy. The differential response of protein sparing to rhGH may explain the disappointing results of some trials of growth hormone use in catabolic patients[32].

As rhGH and insulin may be synergistic in reversing protein catabolism[23] this investigation could be criticized since it proved necessary to treat seven patients with insulin for hyperglycaemia. However, four of the five patients who were randomized to rhGH treatment and who received supplemental insulin were classified as severely catabolic; in these patients rhGH administration resulted in a modest improvement in the rate of NPC. If the remaining patient who received insulin is excluded from the moderately catabolic group, rhGH treatment resulted in an improvement in NPC of 112 per cent in the other four patients. Thus it is unlikely that insulin administration was directly responsible for the improvements in NPC observed in the moderately catabolic patients. However, in contrast to the findings of Liledahl *et al.*[33] and others[24,34], this study has demonstrated that patients with sepsis treated with rhGH may require additional insulin to maintain euglycaemia and to antagonize the hyperglycaemic effects of rhGH. Insulin administration was temporally related to growth hormone treatment and, since the majority of the patients treated with insulin did not have pancreatitis and the insulin treatment was of short duration, it is unlikely that pancreatic failure contributed to the hyperglycaemia observed in these patients.

Growth hormone treatment resulted in lower diastolic, systolic, and mean arterial pressures on days 5–7 of the investigation, while the heart rate and pulse pressure remained unchanged, implying an improvement in cardiovascular efficiency. Growth hormone affects cardiovascular function. At least 50 per cent of acromegalic patients have evidence of left ventricular hypertrophy[35] and growth hormone deficiency is associated with impaired cardiac function both at rest and in response to exercise[36]. The administration of growth hormone to individuals with hypopituitarism improves resting and maximal cardiac performance[37,38]. Growth hormone reduces glucose uptake by adipose tissue resulting in increased circulating levels of free fatty acids and ketone bodies. The increased availability of myocardial specific substrates may lead to a more active myocardium and subsequently to hypertrophy. Growth hormone is known to stimulate amino acid uptake by cardiac muscle cells[39], and synthesis of sulphated mucopolysaccharides and collagen[40]. IGF-I also increases cardiac protein synthesis[41], and the synthesis of cardiac beta myosin heavy chain which plays a primary role in the cardiac contractile apparatus[42,43]. Accordingly, sustained increases in circulating growth hormone or IGF-I may result in an increase in contractile-specific protein synthesis, consequent cardiac hypertrophy and improvement in cardiac function.

It was not possible to demonstrate any difference in daily sepsis score, Karnovsky performance index, Kehlet score, total duration of parenteral feeding or total hospital stay between the treatment groups. However, Ziegler *et al.*[34] and others[24] have reported that courses of rhGH of up to 6 weeks' duration in catabolic intensive care patients enhance respiratory muscle function and may facilitate ventilator weaning.

In conclusion, this study has demonstrated that 7 days of adjuvant rhGH at a dose of 0·3 units per kg per day, in addition to adequate nutritional support, in patients with sepsis is safe and well tolerated. Together with TPN, rhGH rendered the moderately catabolic patient (NPC 1·5 g per kg per day or less) anabolic but rhGH was a less effective anabolic agent in severely catabolic patients (NPC above 1·5 g per kg per day) although a similar increase in circulating IGF-I to that seen in moderately catabolic patients was observed. This suggests that severely catabolic patients are resistant to the protein sparing effects of IGF-I. Significant improvements in physiological function or clinical outcome were not observed in either moderately or severely catabolic patients in response to rhGH. Treatment with rhGH may improve myocardial and cardiovascular function in severely stressed patients and may therefore have a potential role in the haemodynamic management and rehabilitation of the critically ill.

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Long-term results of giant prosthetic reinforcement of the visceral sac for complex recurrent inguinal hernia

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The results of recurrent inguinal hernia repair in a prospective cohort study were evaluated. From May 1986 to December 1990 75 patients with 150 hernias (24 primary, 126 recurrent) were operated using a technique based on Stoppa's preperitoneal mesh repair (giant prosthetic reinforcement of the visceral sac; GPRVS). All patients were at high risk for recurrence: they all had bilateral hernias, mostly bilateral recurrent and often repeatedly recurrent. All patients had a physical examination 1 week, 6 weeks and 1 year after operation. Sixty patients (94 per cent of surviving patients) had a physical examination after a mean follow-up of 5·7 (range 4–9) years. There were no major complications. There was one deep infection that healed without removing the mesh. One of the 75 patients (1 per cent) had a recurrence 2 months after the operation, due to a technical failure. Because of the excellent results, the ease of the procedure and the low complication rate, GPRVS is the authors' operation of choice for any recurrent inguinal hernia.

The traditional anterior approach to the repair of a recurrent hernia carries a high failure rate, from about 5 per cent for the Shouldice technique to more than 30 per cent for other procedures[1,2]. Stoppa and colleagues[3] were the first to combine the preperitoneal approach with the use of a large prosthetic mesh, covering both inguinal areas. Later the procedure became known as giant prosthetic reinforcement of the visceral sac (GPRVS)[4]. The preperitoneal approach avoids scar tissue from previous anterior repairs, and abdominal wall reinforcement is obtained by a large preperitoneal inlay prosthetic mesh rather than by approximation of aponeuroses and muscles. The procedure is therefore ideally suited for the management of recurrent hernias resulting from a weakness of the abdominal wall, especially multiple recurrent hernias and bilateral hernias. These hernias are known to be at high risk for failure after conventional repair[5,6]. Using GPRVS for recurrent inguinal hernias, recurrence rates of 0–5·9 per cent have been reported[4,7–9]. The method of follow-up in these reports varied from questionnaire[9] to physical examination[8], or was not clearly stated[4,7]. It has been shown that follow-up with other than physical examination can fail to detect half of the recurrences[10]. The reported length of follow-up is variable: 1–12 years[7–9] or not clearly defined[4].

The aim of this prospective cohort study was to determine the outcome of GPRVS in a group of consecutive patients with complex recurrent inguinal hernias: bilateral recurrent hernias and recurrent hernias with a primary hernia on the opposite side, with the recurrent hernia often being a multiple recurrent hernia. Postoperative complications and long-term recurrence rates evaluated by physical examination are reported.

Patients and methods

In the period between May 1986 and December 1990 75 patients (74 men) with 150 inguinal hernias were selected for GPRVS because of the presence of a complex recurrent inguinal hernia (bilateral recurrent inguinal hernia, multiple recurrent inguinal hernia with a contralateral primary hernia). Mean(s.d.) age was 65(12) years. A bilateral recurrent hernia was present in 51 patients, and 24 patients had a unilateral recurrent hernia with a primary hernia on the other side. Of the 126 recurrent hernias there were 67 repeated recurrences (*Fig. 1*). Eleven patients had severe chronic obstructive pulmonary disease, six of whom were receiving steroid medication. In all patients previous hernia repairs had been performed through an anterior inguinal approach without the use of a mesh. The exact type of repair could not always be established because some repairs had been performed more than 20 years earlier and because some patients were referred without operative notes.

All patients were operated on under general anaesthesia. Flucloxacillin was given as antibiotic prophylaxis for 24 h. A urinary catheter was introduced to maintain an empty bladder during the operation, and was removed at the end of the procedure.

With a lower abdominal midline incision through the linea alba and the fascia transversalis, access is gained to the preperitoneal and prevesical space. The peritoneal sac is dissected away from the abdominal and pelvic wall, mainly by blunt dissection. The anterior bladder wall is dissected off the pubic bone to the level of the prostate. Laterally the visceral sac is dissected off the iliac vessels, psoas and transverse abdominal muscle (*Fig. 2a*). With this manoeuvre a direct hernial sac is

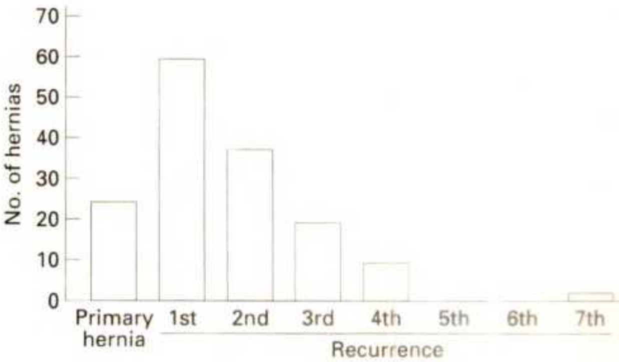

Fig. 1 Number of primary hernias, first recurrences and multiple recurrences

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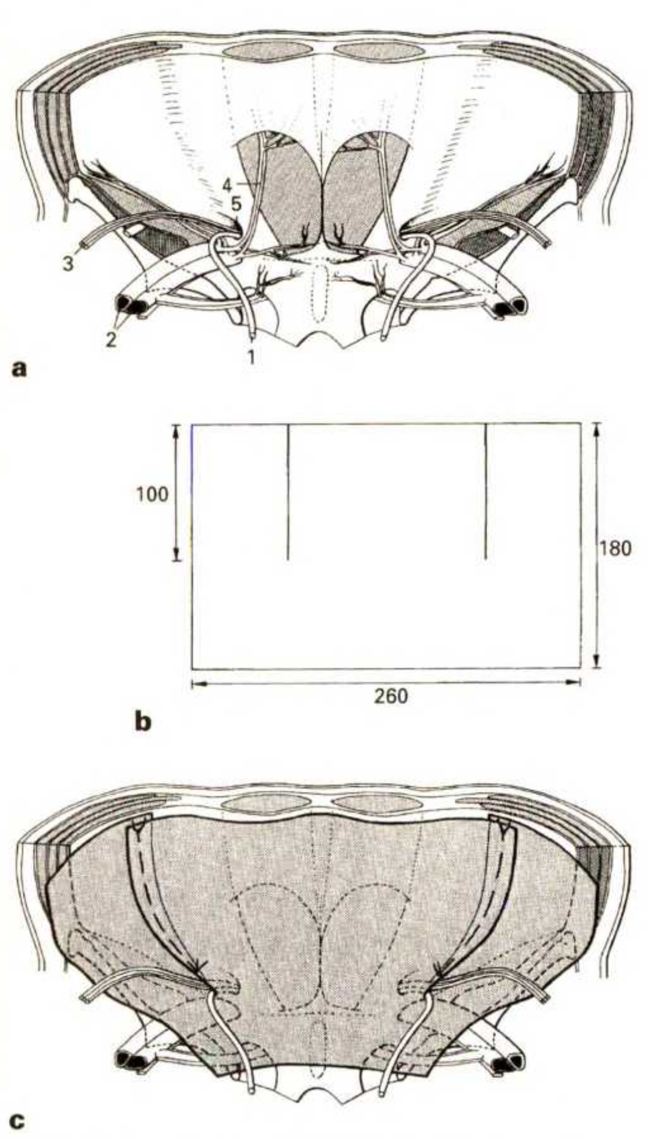

Fig. 2 **a** View of the lower abdominal wall and inguinal region from the inside. Dissection is carried out in this preperitoneal plane. 1, Vas deferens; 2, iliac vessels; 3, testicular vessels; 4, epigastric vessels; 5, deep inguinal ring. **b** Mesh with two vertical slits in the upper border. Dimensions are given in millimetres. **c** The mesh is positioned around the spermatic cord and the slits in the mesh are closed. The mesh covers all inguinal and femoral hernial orifices and prevents an incisional hernia through the linea alba

easily reduced. The spermatic cord is isolated by blunt dissection and a sling is put around it. Any indirect hernial sac is reduced into the abdominal cavity and dissected off the cord. When the distal sac is too large or adherent it is simply divided at the level of the internal ring. The proximal part is closed after repositioning the peritoneal contents and the distal part is left open in the inguinal canal.

When the dissection is complete on both sides, a large rectangular polypropylene mesh (26 × 18 cm) (Marlex; C. R. Bard, Billerica, Massachusetts, USA) with two vertical slits of approximately 10 cm in the upper border (*Fig. 2b*) is positioned around the spermatic cords. The slits are closed with a running polypropylene no. 1 suture (*Fig. 2c*). By overlapping the edges of the slits, the mesh is curved according to the caudal abdominal wall contour and is easier to apply. In an alternative technique, applied in 24 patients, the vas deferens and the spermatic vessels are dissected off the peritoneal sac. The mesh can then be applied between the visceral sac and the parietalized cord elements. In both techniques no attempt is made to close the hernia defect. The mesh is not fixed to any part of the abdominal wall. The midline incision is closed with a running polyglactin no. 1 suture. The mesh covers the caudal part of the parietal peritoneum and bladder. The intra-abdominal pressure pushes and fixes the mesh against the abdominal and pelvic wall. The mesh covers all inguinal and femoral hernial orifices and prevents an incisional hernia through the linea alba. Suction drains are not routinely used.

Operative time, postoperative hospital stay and postoperative complications were noted. Patients were routinely followed by physical examination in the outpatient clinic after 1 and 6 weeks and 1 year after operation. In December 1994 follow-up information on all patients was updated. Medical records of patients who had died were reviewed and the general practitioner was contacted for additional information after the 1-year visit. All other patients were contacted and asked to visit the outpatient clinic for a physical examination by one of the authors.

Results

Mean operative time for the bilateral hernia repair was 39 (range 28–65) min. Median postoperative hospital stay was 5 (range 1–31) days. There were no serious peroperative difficulties. In some patients, mainly after previous abdominal operations, the peritoneal sac was inadvertently entered. These accidental peritoneal openings were always closed meticulously.

Postoperative complications and operative reinterventions are listed in *Table 1*. Most complications were minor. One of the six patients with a postoperative haematoma or bleeding required reoperation. All superficial wound infections were treated conservatively by opening the wound. The only deep wound infection, involving the mesh, was treated by incision and drainage under general anaesthesia. Secondary healing was achieved. All wound infections healed without mesh removal. Two patients developed hydroceles in the first year after surgery, and were treated operatively.

There was one recurrence: a patient who underwent repair of a fourth recurrence on the right and a first recurrence on the left side developed a fifth recurrence on the right side 2 months after operation. Some 2 years later, the recurrent hernia became symptomatic and was repaired using an anterior approach. The mesh was found to be folded to the midline, with the abdominal contents herniating lateral to the mesh. After resection of the hernial sac, the defect was closed by suturing the edge of

Table 1 Postoperative complications and operative reinterventions

Complication	*n*	Reintervention
Postoperative death (0–30 days)	0	0
Pulmonary complications	2	0
Postoperative urinary retention	2	0
Haematoma or bleeding	6	1
Groin seroma	3	0
Superficial wound infection	5	0
Deep infection involving mesh	1	1
Testicular atrophy	0	0
Neuralgia	0	0
Hydrocele (late)	2	2
Total	21	4

the mesh to the inguinal ligament. The patient was examined 4·5 years after this repair, and there was no evidence of recurrence. The other 74 patients were examined by the authors 1 and 6 weeks and 1 year after operation and had no recurrent hernia.

In December 1994 60 patients were examined by the authors after a mean follow-up period of 5·7 (range 3·9–8·9) years. Of these, 53 patients had a physical examination at the outpatient clinic and seven were examined at home or in a nursing institution. No recurrences were detected. Of the remaining 15 patients, 11 had died from unrelated causes. There was no evidence of a recurrence after their latest visit to the outpatient clinic according to medical records and the general practitioner. Of the remaining four patients, three could not be traced and one elderly demented patient was terminally ill at home, with no signs or complaints suggestive of a recurrent hernia. Overall, 60 of 64 surviving patients (94 per cent) had a physical examination by the authors.

Although 15 of 60 (25 per cent) of the patients examined described a feeling of tightness, there were only three (5 per cent) who complained of occasional minor discomfort in the groin region. One patient had had a subsequent Hartmann's procedure for complicated diverticulitis. The lower midline incision through the mesh had been closed with polypropylene and had healed uneventfully. Another patient had a subsequent vascular procedure. Because of fibrosis around the mesh, dissection of the iliac vessels was slightly more difficult.

Patients were uniformly satisfied, and many of those with repeatedly recurrent hernia regretted not having had this operation earlier.

Discussion

In this prospective cohort study of the repair of complex recurrent hernias, at high risk for further recurrence, a recurrence rate of one of 75 patients (1 per cent) or one of 150 hernias (0·7 per cent) was achieved. The only recurrence in this series resulted from a technical failure, and was apparent 2 months after operation. This finding supports the view that failures after GPRVS occur early in the postoperative course, and are mainly due to surgical technique[4,11]. When the mesh is properly positioned and becomes solidly fixed to the surrounding tissues, recurrences are unlikely.

This study supports the conclusion of other surgeons that GPRVS provides a definitive cure of inguinal hernias[4,7–9]. Because of the excellent results, ease of the procedure and low complication rate, GPRVS has now become the authors' operation of choice for any recurrent inguinal hernia.

Because of an initial fear of infectious complications with the use of foreign material, the GPRVS procedure was reserved for patients with complex recurrent inguinal hernia. Although the 8 per cent incidence of infectious wound complications in this series is higher than that of 1 per cent for anterior mesh repair[12,13], it has never been a serious problem. The five superficial wound infections were managed on an outpatient basis and the single deep infection involving the mesh was treated adequately with incision and drainage without mesh removal. Polypropylene is known to be very resistant to infection, and infected wounds with exposed mesh most often heal without removal of the mesh[12,14,15]. For this reason polypropylene is the mesh material of choice, although other surgeons prefer polyester meshes[4,7].

A laparotomy can easily be performed through the mesh. To prevent an incisional hernia through the incised mesh, the abdominal wall is closed with non-absorbable suture material (polypropylene). Access to preperitoneal and retroperitoneal structures such as the ureter, bladder, prostate and iliac vessels can be slightly impeded because of fibrosis around the mesh but, in the authors' experience, this presents no real difficulty.

Patient satisfaction was remarkably high in this series. After multiple unsuccessful bilateral procedures patients sometimes had lost all hope of cure of their inguinal hernia. Some patients reported that they had been crippled for years, and were now able to do heavy labour again.

Most methods of laparoscopic hernia repair are based on the principle of GPRVS. With application of a preperitoneal mesh widely overlapping the edges of the defect laparoscopic hernia repair combines the best of both worlds: a sound repair with a low recurrence rate and low postoperative morbidity achieved with a less invasive technique. Because of the small access wounds and the inherent no-touch technique, a lower infectious complication rate can be expected. This is supported by preliminary reports[16–18]. The present study validates the principle of a large inlay mesh repair, on which laparoscopic hernia repair is based. Results of randomized trials are awaited for proper evaluation of laparoscopic hernia repair[16,19]. In the meantime, GPRVS remains the authors' gold standard for the repair of recurrent inguinal hernia.

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Transanal endoscopic microsurgery – initial experience from three centres in the United Kingdom

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Over a 28-month period, 100 transanal endoscopic microsurgical excisions of rectal tumours were carried out in three centres. The histological diagnosis was benign adenoma in 77 and invasive adenocarcinoma in 23. Complete excision of the tumour with histological confirmation was achieved in 70 (91 per cent) of the adenomas and in all but one of the carcinomas. Of the carcinomas, 18 were recognized before operation and the remaining five were diagnosed on postoperative histology. Of the patients with carcinoma, one had immediate further surgery, nine had radiotherapy and 13 had no extra treatment. To date, four patients have had a recurrence of villous adenoma, and two of the patients treated for invasive carcinoma have had local recurrence. These initial results of transanal endoscopic microsurgery in the UK compare well with those of earlier reports, indicating that the technique has a useful place in the management of sessile adenomas of the mid and upper third of the rectum, and of some carefully selected carcinomas.

Adequate transanal excision of pedunculated or small sessile benign rectal tumours can be achieved easily by snare diathermy but large sessile adenomas present a more challenging problem. In addition, transanal excision of rectal carcinoma may be appropriate treatment in a proportion of patients[1,2], and this can also be technically demanding.

Methods designed to achieve complete excision of large rectal tumours by the transanal route have generally employed anal retractors[3], and the resultant visualization and access are often far from ideal. Endoscopic treatment using a resectoscope has been advocated recently[4] but, although effective, complete tumour excision is difficult to ensure as the tumour is removed piecemeal. In the 1980s, however, Buess and Mentges[5] developed transanal endoscopic microsurgery (TEM) using a specially designed operating sigmoidoscope. This device incorporates a high-quality binocular optical system and pressure-regulated insufflation with continuous suction, which provide excellent visualization and a greatly improved operating environment.

Although TEM has been available for over 10 years it was only introduced to the UK in 1993[6]. The initial results from three centres that have adopted the technique are presented.

Patients and methods

In a 28-month period, 100 patients underwent TEM for rectal tumours in three centres in the UK. During this time, all patients with a preoperative diagnosis of benign rectal adenoma deemed unsuitable for complete excision by snare diathermy and a small number of patients with known invasive adenocarcinoma were treated. In addition to the 100 patients who underwent the procedure, a further eight were initially selected for TEM but at operation were found to be unsuitable. Fifty-three of the patients who had TEM were men; the mean age was 70·1 (median 71, range 29–95) years.

TEM was carried out using the equipment developed by Buess and manufactured by Wolf (Knittlingen, Germany) (*Fig. 1*). This is based on an operating sigmoidoscope 12 or 20 cm in length and 4 cm in outer diameter, which incorporates a high-quality binocular optical system providing up to ×6 magnification. Rectal distension to a pressure of 10 mmHg with simultaneous continuous low-pressure suction is achieved by means of a combined endosurgical unit incorporating pressure-sensitive insufflation of carbon dioxide and a roller suction unit. Submucosal or full-thickness tumour excision is achieved by means of a diathermy knife and graspers introduced through gas-

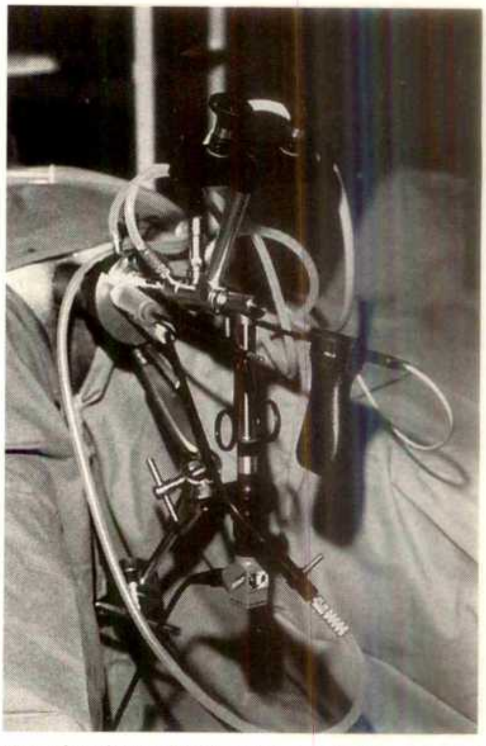

Fig. 1 Transanal endoscopic microsurgery equipment set up for use

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tight operating ports on the occlusive operating face plate of the sigmoidoscope. The subsequent defect can then be closed with 3/0 polydioxanone, using a purpose-designed needle holder and securing the suture by means of a silver clip.

The apparatus is supported by a multijointed Martin arm which allows repositioning of the sigmoidoscope during the procedure, but it is important to have the patient in the correct position at the outset. The Lloyd-Davies or lithotomy position is ideal for a tumour on the posterior wall of the rectum, but for anterior lesions the patient is placed face down with the hips flexed and the legs apart. Occasionally it is necessary to operate with the patient in the right or left lateral position.

Results

Of the 100 patients, 82 had a preoperative histological diagnosis of benign adenoma, although five proved to have invasive carcinoma in the resection specimen (three T_1 and two T_2 tumours). Eighteen patients had a preoperative diagnosis of carcinoma. The mean height of the tumour above the anal verge was 7·9 (median 8, range 1–20) cm, and the mean maximum diameter of the lesion was 4·1 (median 3·0, range 1–14) cm. The tumour position within the rectum was classified as posterior in 45, anterior in 21, left lateral in 15, right lateral in 12 and circumferential in seven.

Adenomas

Seventy-seven patients had a postoperative diagnosis of benign adenoma, and in 70 (91 per cent) complete excision of the tumour was confirmed histologically. These patients have been followed up for a mean duration of 7·4 (median 6, range 0–24) months, and to date four recurrences have been detected. Three of the recurrences occurred in patients whose operations had been performed for recurrent disease; only two had a histologically incomplete excision.

Carcinomas

Twenty-three patients had a postoperative diagnosis of invasive carcinoma; the pathological stage was T_1 in seven, T_2 in 14 and T_3 in two. The mean follow-up in this group of patients was 6·7 (median 6, range 0–24) months. Four of the T_1 tumours were diagnosed before operation, all were completely excised and none had any further treatment. Of the 14 T_2 tumours, 12 were diagnosed before surgery on biopsy and transrectal ultrasonography, and all but one were completely excised. The patient with incomplete excision subsequently underwent abdominoperineal excision of the rectum and was found to have residual tumour in the resection specimen. Nine of the others had adjuvant radiotherapy, as this has been shown to reduce the risk of local recurrence[7]. Six patients had preoperative contact radiotherapy[8]. Four patients with T_2 tumours and the two with T_3 tumours have had no further treatment because of age and infirmity. Two patients with T_2 tumours have had salvage abdominoperineal resection for recurrent disease after apparently complete excision, and are currently tumour-free. (*Table 1*). All patients with T_{2-3} tumours were elderly (mean age 79 (range 62–94) years) and were considered high-risk candidates for abdominal surgery.

Table 1 Postoperative histology and recurrence after rectal excision by transanal endoscopic microsurgery

Postoperative histology	No. of lesions	Complete histological excision	Recurrences to date
Adenoma	77	70 (91)	4 (5)
Carcinoma			
T_1 carcinoma	7	7 (100)	0 (0)
T_2 carcinoma	14	13 (93)	2 (14)
T_3 carcinoma	2	2 (100)	0 (0)

Values in parentheses are percentages. Of the patients with T_2 carcinoma, one had incomplete excision and two had subsequent recurrence. All three were treated by salvage surgery

Complications

In six patients, all with high anterior tumours, the peritoneal cavity was breached during the procedure. In five cases the defect was closed with sutures from within the rectum, and there were no further postoperative complications. In one patient, however, it was necessary to convert to an anterior resection. Two patients suffered from transient incontinence to liquid and gas, and one patient developed a rectal stenosis which required dilatation. One patient died on the seventh postoperative day from myocardial infarction.

Operating times and hospital stay

The mean operating time was 79 (median 60, range 30–240) min, and median hospital stay 4 (range 1–21) postoperative nights.

Unsuccessful attempted procedures

In eight patients with a preoperative diagnosis of adenoma excision by TEM was intended but proved impractical at operation. In two cases, the lesion was too low, preventing an adequate seal around the sigmoidoscope and allowing leakage of carbon dioxide; these patients were treated by conventional transanal submucosal excision. In one patient, the lesion was high on the anterior wall, and anterior resection was performed. In four patients, the tumour was so polypoid that adequate visualization for TEM was impossible. In these patients, the tumour was removed by snaring; complete excision was achieved in two by this means, and in the other two a subsequent excision of residual tumour by TEM was performed. TEM was also attempted in one patient with local and disseminated recurrence after anterior resection, but was unsuccessful because of a radiation stricture in the rectum.

Discussion

Sessile benign rectal tumours that are not a suitable shape or size for snare diathermy excision are still often amenable to removal by the transanal route. This can be performed by means of piecemeal excision or, preferably, by a formal submucosal or full-thickness 'disc' excision incorporating a margin of normal tissue to ensure complete clearance of the neoplastic tissue. Although the former technique is usually performed endoscopically, it has been customary to carry out the latter by means of anal retractors using the method of Parks[3], which is limited to the lower third of the rectum.

Table 2 Published series of conventional transanal excision of rectal adenoma

Reference	Year	Technique	No. of patients	Histological clearance (%)	Malignancy (%)	Duration of follow-up	Morbidity (%)	Recurrence (%)
Parks and Stuart[14]	1973	Submucosal excision	30	n.a.	17	6 months–10 years	0	10
Nivatvongs *et al.*[16]	1973	Submucosal excision	53	n.a.	5·6	0–10 years	3·7	9·4
Thomson[15]	1977	Various techniques	106	n.a.	0	0–10 years	9·5	17·9
Pollard *et al*[17]	1988	Various techniques	70	n.a.	0	0–18 years	n.a.	13
Sakamoto *et al.*[18]	1991	Various techniques	117	n.a.	0	0–15 years	14·5	27·3

n.a., Data not available

However, with the development of TEM by Buess and colleagues, it is now possible to carry out formal transanal resection by means of an endoscope, which affords excellent access and vision. TEM thus might be expected to yield better results than the traditional methods both in terms of completeness of excision and recurrence rates. Unfortunately, however, the scanty data available from the literature make comparisons difficult. There are several reported series describing the removal of sessile tumours of the rectum and colon, but many of these deal mainly with colonoscopic excision of colonic tumours, and provide few data on rectal lesions[9–13].

Some useful information is available, however. Parks and Stuart[14] described 30 cases of transanal submucosal excision of villous adenoma, five of which had malignant change and four of which required more extensive surgery. The overall recurrence rate was 10 per cent with a mean follow-up of 3 years. Other series report recurrence rates of between 9·4 and 27·3 per cent[15–18]; these are summarized in *Table 2*. In none of these series, however, was complete excision confirmed by histological evidence from the resection specimens.

Although it is often difficult to be sure about the precise techniques used or the rates of complete excision at the time of operation, it is clear from the literature that recurrence rates after transanal excision of rectal adenoma are high. In contrast, Buess and Mentges[5], who treated 229 rectal adenomas by TEM excision between July 1983 and June 1991, reported a recurrence rate of 8·7 per cent, 3 per cent at the site of the previous lesion and 5·7 per cent at distant sites within the rectum. Likewise, another series of 24 patients treated by TEM for benign rectal tumours has reported a nil recurrence rate, albeit with a short period of follow-up[19]. In the present series the overall recurrence rate was 5 per cent and, although the duration of follow-up was short, it is reassuring that the complete excision rate was 91 per cent.

Another advantage of TEM is that it gives access to tumours that are not suitable for conventional treatment by virtue of their position within the rectum. Traditionally such tumours are treated by means of anterior resection, the trans-sphincteric approach of Mason[20] or the presacral operation of Kraske[21]. These procedures are all associated with greater morbidity rates than transanal excision, and Buess' results[5] indicate that TEM can be used to deal with tumours up to 24 cm from the anal verge. In the present series the position of the tumour ranged from 1 to 20 cm from the anal verge with a median of 8 cm. Although about 20 per cent of these cases may have been quite suitable for conventional transanal surgery, we contend that TEM offers a more precise means of excision, and it certainly increases the proportion of tumours amenable to transanal excision.

Another more controversial area is the role of transanal surgery in the treatment of invasive carcinoma. If tumours are carefully selected using criteria developed by Morson[1] (i.e. completely excised, no extramural invasion and moderately to well differentiated), then local excision alone is associated with good survival and an acceptable risk of local recurrence[2,22]. It is also possible to excise more advanced tumours locally and, although this is associated with much higher recurrence rates, radiotherapy may improve the results[7,8,23]. TEM is ideally suited to local excision of invasive malignancy[19,24] and should prove an extremely useful technique in the development of this approach. It must be stressed, however, that TEM with curative intent can only be justified for T_1 tumours at present. The place of local excision with adjuvant radiotherapy for T_2 tumours has yet to be defined, and appropriate clinical trials are awaited with interest. Some elderly or frail patients can, however, be offered TEM where the alternative of major abdominal surgery is unreasonable.

Whatever the indication, transanal surgery causes less morbidity than transabdominal approaches to the rectum. Complications do occur, however, and the commonest are bleeding, perforation, incontinence and rectal stricture. As can be seen from *Table 2*, the overall complication rate for conventional transanal surgery in reported series varies from 0 to 14·5 per cent, compared with 6·5 per cent for TEM reported by Buess and 9 per cent for the present study. It is of interest that postoperative bleeding is unusual with TEM, whereas it accounts for over half of the complications reported in other series. Perforation, on the other hand, can be a significant source of morbidity with TEM. Presumably the excellent vision afforded by TEM allows more precise haemostasis, whereas the ability to excise high rectal lesions increases the likelihood of perforation, especially when the tumour is anterior, and thus more likely to be above the peritoneal reflection. In this series, all perforations were in high anterior tumours, and in three cases the tumour was recurrent making identification of the submucosal plane difficult. All of the perforations were recognized and all but one were managed by immediate endorectal suturing. If perforation does occur during conventional transanal surgery it may not be seen easily and, even if it is, closure without laparotomy may not be possible.

In conclusion, this initial experience with TEM has been favourable, at least in terms of ability to achieve histologically complete excision of rectal tumours. Further follow-up will be required to assess its impact on recurrence rates for benign adenoma, and its role in the treatment of invasive malignancy has yet to be defined fully. The authors believe, however, that TEM represents a significant advance, and surgeons who see substantial numbers of tumours suitable for transanal excision should consider using this technique.

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Prospective study of the proctographic and functional consequences of transanal endoscopic microsurgery

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A prospective study of clinical, manometric and proctographic results in 36 patients presenting for transanal endoscopic microsurgery was performed. Anorectal manometry showed no difference in maximal squeeze pressure before and 12 months after operation, but resting pressures were lower after surgery (mean(s.e.m.) preoperative 86·1(27·6) mmHg *versus* postoperative 67·2(23·2) mmHg, $P<0{\cdot}05$). The rectoanal inhibitory reflex was lost in a significant group of patients (reflex present in 34 of 36 patients before operation and in 27 of 36 12 months after operation, $P<0{\cdot}05$). Proctography, manometry and questionnaire showed preserved function of most modalities 12 months after operation such that if objective function was impaired clinical function was adequate.

Transanal endoscopic microsurgery (TEM) was developed in 1983[1] and many patients have been treated using this technique. The majority of clinical research has described technological advances, safety and adequate oncological outcomes[2–6]. Functional results of TEM have not been investigated as fully despite this being an important aspect, particularly in comparison to the results of low anterior resection or trans-sphincteric surgery[7–8]. A prospective study of clinical, manometric and proctographic parameters was, therefore, undertaken in patients presenting for TEM.

Patients and methods

A prospective clinical study design was used in 42 patients undergoing TEM for adenoma and (ultrasound diagnosed) uT1 tumours between 1991 and 1993. A clinical questionnaire was administered and anorectal physiology and manometry were performed before operation and 12 months after surgery. Proctography was performed at the same time points but six patients did not have a complete study or the results were not available. Data for 36 patients are therefore presented. There were 26 men and the age range was 45–81 years (mean 66·7 years).

Transanal endoscopic microsurgery

This was performed using a standard protocol as described fully elsewhere[3].

Anorectal manometry and physiology

Anorectal manometry was performed using a high-pressure low-compliance system (Arndofer Medical Specialities, Greendale, Wisconsin, USA), an eight-channel water perfused catheter with sideholes 5 mm and 45° apart (outer diameter 3·8 mm, perfusion rate 0·5 ml/min; Arndofer Medical Specialities) and an inflatable balloon at the tip (Brothitan, Hochstadt, Germany). Resting anal pressure and the length of the anal high-pressure zone were determined by a continuous pull-through method (1 mm/s). Rectoanal inhibitory reflex and thresholds for first sensation, urgency and maximum tolerable volume were determined. Rectal compliance was determined at the maximum tolerable volume as described previously[9].

Clinical questionnaire

The standardized interview and the patient's diary contained questions concerning stool frequency, continence to flatus, liquid and solid stool, use of sanitary pads, ability of stool discrimination and ability to defer dafaecation. For continence and stool discrimination, the patients allocated answers to the categories 'always', 'partly' and 'never'; for the use of pads to the categories 'no' or 'yes'; and for the ability to defer defaecation patients had to choose between four categories: delay of less than 1 min, 1–5 min, 5–10 min and more than 10 min.

Proctography

Only thirty-six patients had complete baseline and follow-up proctograms. Standard proctography was performed as described in detail elsewhere[10]. A radio-opaque ruler was used to improve the precision of measurements from still films, which were selected from the dynamic study by the radiologist. These were independently read by two investigators and perineal and pelvic floor descent measured during rest and defaecation. The two values were subtracted to give relative descent values. Anal canal length was recorded. The anorectal angle was measured at rest using the rectal centroid to anal axis angle. The pelvic floor was drawn between the upper point of the os pubis and the coccyx. Rectocele, intussusception, postoperative distortion and stricture were noted and comparisons made between preoperative and postoperative appearances.

Statistical analysis

For calculations of squeeze pressure and resting pressure, the respective maximum value of the eight channels was used. The qualitative answers of the interview and the diary were evaluated by attributing score points to the categories as follows: 'always' = 2, 'partly' = 1 and 'never' = 0; 'more than 10 min' = 3, '5–10 min' = 2, '1–5 min' = 1, and 'less than 1 min' = 0. Proctography was analysed by a scoring system in which 'gross anatomical abnormalities and/or both pelvic/perineal descent and anorectal angle abnormal' = 0; 'small anatomical abnormalities and/or either one of pelvic/perineal descent or anorectal angle abnormal' = 1; 'normal proctogram' = 2.

For the entire study group preoperative and postoperative values of anorectal manometry, stool frequency and proctography were compared by Wilcoxon's test for paired data.

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Qualitative preoperative and postoperative data from the interview were compared by χ^2 test.

Results

Results of transanal endoscopic microsurgery

Histology in all 36 patients showed a tubulovillous adenoma. Mean(s.e.m.) tumour distance from the anal verge was 9·4(2·9) cm (range 2–18 cm). The mean excised area was 21 (range 2–104·5) cm^2.

Thirty patients had one or two adjacent quadrants of the circumference involved with tumour. Six patients had three or four quadrants involved.

The mean operating time was 90 (range 30–330) min. Thirty patients had full-thickness rectal wall excision and six either a mucosectomy or partial wall excision. Six patients had complications: five had suture dehiscence which was managed conservatively with no adverse sequelae and one had a haemorrhage that required reoperation and endoscopic haemostasis.

Completeness of emptying

The proctographic data did not show gross differences after TEM. Pelvic floor and perineal descent was sometimes improved but this did not reach statistical significance (*Table 1*). The preoperative and postoperative anorectal angle showed a 30–40° increase between rest and defaecation. Thirty-four of 36 of the films obtained after defaecation showed complete evacuation (less than 10 per cent residual contrast present on film). Anorectal angles were not impaired even if the lesion was excised from this area. Silver clips were still present in 30 of 36 patients at 12 months and provided a useful guide to the site of excision.

Rectoanal inhibitory reflex, compliance and stricture

Rectoanal inhibitory reflex was lost in seven patients. There was no correlation between this and the proctographic appearance. Although rectal compliance was only assessed in 15 of the 36 patients this showed a significant reduction 12 months after operation. Rectal compliance represented the only incomplete data set. In the six patients with near or full circumferential tumours TEM did not create strictures or distortion in the postoperative proctogram. All three patients with a rectocele on proctography before and after TEM reported the sensation of incomplete evacuation of stool.

Table 1 Proctographic and manometric data from 36 patients

	Baseline	12 months after operation	P*
Pelvic floor descent (cm)	2·65(0·6)	2·55(0·7)	n.s.
Perineal descent (cm)	3·85(0·7)	3·82(0·8)	n.s.
Anorectal angle (°)	109·8(7·8)	108·7(6·9)	n.s.
Anal resting pressure (mmHg)	86·1(27·6)	67·2(23·2)	<0·05
Squeeze pressure (mmHg)	164·8(58·2)	173·5(71·8)	n.s.
No. with rectoanal inhibitory reflex present	34	27	<0·05

Values are mean (s.e.m.). *Wilcoxon's test for paired data. n.s., Not significant

Table 2 Questionnaire data for 36 patients (actual patient numbers)

	Baseline	12 months after operation	P*
Continence to flatus	30	28	n.s.
Continence to liquids	27	23	0·08
Continence to solids	34	34	n.s.
No use of sanitary pads	31	29	n.s.
Defer defaecation >10 min	31	28	n.s.
Stool discrimination	34	30	n.s.

Values are mean. **t* test. n.s., Not significant

Table 3 Proctographic and manometric data of four patients who showed postoperative improvement in proctographic appearance

	Baseline	12 months after operation
Pelvic floor descent (cm)	3·45(0·8)	2·35(0·7)
Perineal descent (cm)	5·95(1·1)	3·75(0·6)
Anorectal angle (°)	113(6·2)	104·5(9·6)
Anal resting pressure (mmHg)	85(15·2)	67·5(17·1)
Squeeze pressure (mmHg)	157(36)	220(96)
No. with rectoanal inhibitory reflex present	3	2

Values are mean (s.e.m.)

Continence to gas, liquid and solid (Table 2)

Overall, continence to solid stool and flatus was not affected after operation. The threshold volume required to elicit first sensation was reduced at 12 months (mean(s.e.m.) preoperative 66·5(37·6) ml *versus* postoperative 51·2(33·4) ml, $P<0·05$) but the volume needed to elicit urgency and the maximum tolerable volume were not significantly different.

In no patient was the proctographic data obtained 12 months after operation worse than the preoperative data: four of 36 patients with complete proctograms showed an improvement after operation either in gross morphology of the proctogram or in analysis of individual parameters (*Table 3*).

Discussion

TEM does not have major deleterious effects on anorectal function. Stretching of the sphincters to insert the rectoscope resulted in reduced resting pressures at 12 months but did not affect continence and symptoms. Proctography showed minimal or no distortion at the operative site after 1 year. In some patients the degree of pelvic floor and perineal descent was improved after TEM; this may be due to either perirectal fibrosis or the effect of rectal mucosal excision reducing prolapse. The clinical significance of this finding is unclear.

TEM has not been directly compared with an alternative treatment such as low anterior resection in a prospective randomized setting. Since only adenomas and early carcinomas are suitable for TEM and the treatment of some early adenomas by anterior resection might be unnecessarily radical, randomization would be difficult. Statistical comparison with historical controls would be unsatisfactory and the study therefore correlated the functional and proctographic results of TEM.

Completeness of emptying was not affected by TEM; this is important since, although there was some reduction in compliance in certain patients, this was not translated into functional impairment. The extent of tumour assessed by circumferential involvement did not affect either compliance or emptying.

Structural problems, such as stenosis, intussusception or rectocele, were not evident after TEM. Local transmural surgery without microsurgical conditions may produce strictures[1].

Continence was essentially unimpaired at 12 months other than for liquid stool and this may have been due to stretching of the sphincters. Terminal pudendal nerve latencies were not measured, however, in this study. Alternatively, the underlying mechanism may have been loss of the rectoanal inhibitory reflex with constipation and overflow.

The methodology used in this study may not have demonstrated residual functional deficits but the combination of accurate manometry, proctography and questionnaire has been used by many groups to investigate the results of other colorectal procedures[9–13]. Proctography performed earlier in the postoperative period may have revealed transient abnormalities but this was not considered feasible. It has been shown previously that baseline anorectal angle, perineal descent and puborectalis length vary between the left lateral decubitus and seated positions. Variations such as this may reduce the reproducibility, and hence clinical importance, of this investigation[10]. In the present study, all proctography was performed with the patient in the seated position.

In conclusion, anorectal function is well preserved in patients who have undergone TEM and any symptomatic or physiological impairment is usually transitory and resolves within 12 months.

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Mesorectal excision for rectal cancer

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A series of 103 consecutive rectal cancers was prospectively documented. Laparotomy was performed in 78 patients of whom five did not undergo resection. Resection was considered curative unless there were liver metastases or biopsy-proven residual disease. Nine patients had a palliative resection. Thus 64 patients underwent a curative resection, 52 (81 per cent) of whom had an anterior resection of which 26 (46 per cent) were performed by trainees. There were three deaths after operation. Eight (14 per cent) patients developed a clinical anastomotic leak. Thirty patients were available for a minimum follow-up of 24 (mean 33, range 24–49) months. Four (13 per cent) patients developed distant recurrence. There were no isolated pelvic or anastomotic recurrences. One patient with distal recurrence may have had pelvic disease. The cumulative recurrence-free survival rate at 24 months was 84 per cent. These results support the suggestion that mesorectal excision may reduce local recurrence.

Heald and colleagues[1] first published their results of mesorectal excision during surgery for rectal cancer in 1982. The low local recurrence rate initially reported has withstood the test of time[2,3], and the results have generated much debate[4,5] The true value of mesorectal excision will be established only if other surgeons can achieve a low recurrence rate[5]. To date, there has been no such prospective report.

The author, a general surgeon, has visited Mr Heald's unit and practises the technique of mesorectal excision[6]. This study reports the outcome for patients under the author's care.

Patients and methods

Details of patients with rectal cancer referred to the author were prospectively recorded on a microcomputer (Macintosh, Apple, Cupertino, California, USA) using a bespoke database (FileMaker, Claris, Santa Clara, California, USA). Appropriate clinical, operative, pathological and follow-up data were recorded. Recurrence-free survival was calculated by the method of Kaplan–Meier.

Between November 1989 and March 1995, 103 consecutive patients referred to the author underwent surgery for their first rectal cancer. Nine patients had transanal resection and 16 did not undergo laparotomy because of advanced cancer (11) or severe concomitant disease (five). The remaining 78 patients underwent laparotomy (*Table 1*). Mean age was 70·1 (36–95) years. The remaining 57 who underwent anterior resection are now discussed.

Table 1 Operative procedure in patients undergoing laparotomy

		Operation		
	Comment	Other	Anterior resection	Abdomino-perineal resection
No resection				
Laparotomy only	Liver metastases	1		
Loop colostomy	Advanced local tumour and liver metastases	3		
	Irresectable local tumour	1		
Palliative resection				
Liver metastases	Segmental resection	1	5	1
Local residual cancer	Biopsy proven			1
Perforation	Emergency Hartmann's procedure	1		
Curative resection			52	12
Total		7	57	14

Definitions

(1) This was a consecutive series of patients. None was excluded on the basis of presentation. Operations by surgeons of all grades are included.

(2) The lower border of the tumour was measured from the anal verge with a rigid sigmoidoscope. In most cases the patient was in the left lateral position but in a few the height was recorded in the lithotomy position during an examination under anaesthesia. Tumours with a lower border between 12 and 16 cm were defined as rectosigmoid.

(3) Operations in which resection was undertaken were considered curative unless there were multiple liver metastases, biopsy-proven single liver metastasis or histological evidence of residual cancer in biopsy specimens from the tumour bed. When there was clinical suspicion of residual disease the closest margin of the specimen was marked with a suture to direct pathological examination.

(4) Patients remain under regular surveillance. The duration of follow-up was calculated from the date of surgery to the date of last review. A patient was considered free of cancer if the clinical assessment, including sigmoidoscopy, was normal. Routine surveillance colonoscopy was performed 12 months after surgery. Radiological investigations were undertaken if there was clinical suspicion of recurrent disease or if the level of carcinoembryonic antigen increased to more than 70 units/l.

Surgical technique

The surgical technique during anterior resection aimed to reproduce that previously described[6]. In brief, the colon was routinely mobilized from the mid-transverse colon to the sigmoid colon with a high tie of the inferior mesenteric vein and artery. The colon was divided and only then was the tumour palpated. The rectum was mobilized with sharp dissection. If anterior resection was planned the mesorectum was either divided 5 cm below the tumour or, for low tumours, completely excised. Before anastomosis the rectum was cross-clamped and washed

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out with aqueous povidone–iodine (Betadine; Napp Laboratories, Cambridge, UK). Both hand-sewn (including three coloanal anastomoses) and stapled (but not 'double stapled') anastomoses were employed. The pelvis was washed out with tetracycline solution (1 g/l).

Results

Twenty-six anterior resections (46 per cent) were performed by surgeons in training (*Table 2*). Five patients had a covering stoma raised. Eight patients (14 per cent) had a clinical anastomotic leak. Five had liver metastasis resulting in 52 curative anterior resections. Four patients had a contiguous organ resected *en bloc* with the tumour (uterus (one), bladder (partial) (one), seminal vesicles (two), appendix (one)). In two of these patients and in two additional patients the cancer was adherent to the pelvic side wall. None of these patients had biopsy-proven residual disease and all were therefore considered to have undergone curative resection.

Three patients died within 30 days of curative surgery. Two patients, aged 79 and 87 years, died from severe pre-existing cardiorespiratory disease and one as a direct result of anastomotic leak.

Dukes stage for the 52 tumours resected by curative anterior resection was: A in 11 (21 per cent), B in 22 (42 per cent) and C in 19 (37 per cent). The equivalent TNM (tumour node metastasis) classification for the tumour was pT1 in four, pT2 in 18, pT3 in 27 and pT4 in three. Dukes stage for the 30 anterior resections with at least 24 months of follow-up was A in five, B in 15 and C in ten.

Adjuvant therapy

Three patients who had a subjectively palliative local resection underwent postoperative radiotherapy. Both patients with at least 24 months of follow-up developed complications after radiation treatment.

Follow-up and survival

Six patients (12 per cent) who survived a curative anterior resection subsequently developed distant metastatic colorectal cancer. The median elapsed time from surgery to recurrence was 7 (range 4–13) months. Five of the six had unfavourable histological features (four Dukes stage C, four extra-nodal mesenteric deposits, three poor differentiation, three intravenous invasion and one perineural invasion).

Thirty patients who had curative anterior resection and were alive at 30 days were available for a minimum follow-up of 24 (mean 33, range 24–49) months. Four developed distant metastases (mean elapsed time 9 (range 5–12) months) and subsequently died from cancer (*Table 3*). Three further patients were cancer-free when they died from an unrelated cause. The cumulative recurrence-free survival rate at 24 months was 84 per cent (*Fig. 1*).

Table 2 Surgeon and assistant at anterior resection

Surgeon/ assistant	Height from anal verge (cm) 0–4·0	4·1–8·0	8·1–12·0	12·1–16·0 (recto-sigmoid)	Total
Consultant	2	14	10	5	31 (54)
Senior registrar/ consultant		5	3	2	10 (18)
Other trainee/ consultant		3	3	2	8 (14)
Senior registrar/ other trainee		1	1	4	6 (11)
Other trainee/ other trainee				2	2 (4)
Total	2	23	17	15	57

Values in parentheses are percentages

Table 3 Outcome after curative anterior resection in patients available for a minimum follow-up of 24 months

	Present series	Heald *et al.*[1]
Mean (range) follow-up length (months)	33 (24–49)	36 (24–46)
Mean height from anal verge (cm)	10·0	8·9
Patients having an anterior resection (curative and palliative)	32	65
30-day mortality (curative and palliative anterior resections)	0	5 (7·7)
Curative anterior resection	30 (94)	50 (83)
Procedure performed by trainees	13 (43)	0
Dukes C cancer	10 (33)	10 (20)
Metastasis		
Distant only	3 (10)	6 (12)
Distant and pelvic	1 (3)	0
Suture line	0	0
Death from recurrent colorectal cancer	4 (13)	3 (6)

Values in parentheses are percentages

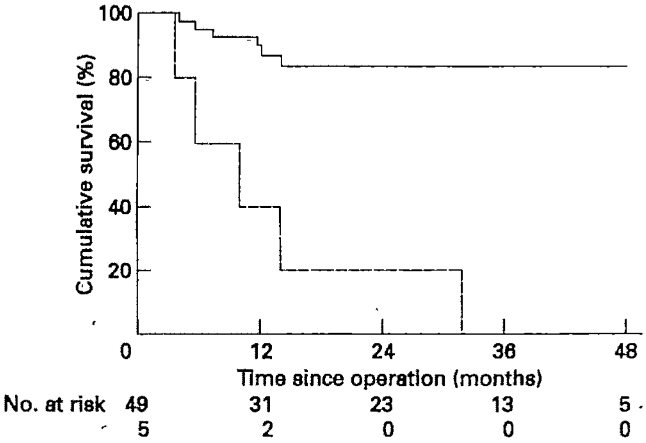

Fig. 1 Cumulative recurrence-free survival curve for 52 patients who underwent curative anterior resection (84 per cent at 24 months). Deaths within 30 days are excluded (———). Overall survival curve for five patients who had palliative anterior resection (– – –)

Local recurrence

No patient undergoing curative anterior resection developed an isolated deep pelvic or anastomotic recurrence. One patient who developed distant metastases may also have had a pelvic recurrence. The anastomosis leaked after resection of a Dukes C (pT4) cancer and 12 months later the patient developed pulmonary and liver metastasis. The patient died 10 months later from pulmonary embolus secondary to a presumed deep vein thrombosis. This clinical background was such that, in the absence of a post-mortem examination, pelvic recurrence was assumed.

Discussion

Comparative audit is fraught with difficulties. Because Heald and colleagues' results[1–3] were superior to those previously published they prompted much debate[5], and indeed scepticism[4]. Such doubts will be answered only if other surgeons who perform a mesorectal excision are prepared to report their own results[5]. To date, there has been no such prospective report.

It would take many years for most general surgeons to recruit and follow up a large series of rectal cancers. The 2-year results of Heald and colleagues[1] have withstood the test of time[2,3] and it would seem reasonable for others to use them as an indicative benchmark. The results of the present series are similar to those of Heald *et al.*[1] and support the concept of mesorectal excision (*Table 3*). Local recurrence was virtually eliminated. The proportion of patients developing distant metastases in this series was comparable despite there being 60 per cent more patients with Dukes C cancer. The proportion of advanced cases in this series is similar to that of other surgeons working around Edinburgh[7].

Although the present series is smaller than the initial report of Heald and colleagues, there are several specifically relevant differences:

(1) this study was a consecutive series of all referred patients;
(2) it is unlikely there was any external referral or selection bias;
(3) all resections were considered locally curative unless there was histological evidence of residual tumour; and
(4) almost half the anterior resections were performed by trainees.

There was a technical difference from the description of Heald *et al.* in that a total mesorectal excision was performed only when the cancer had its lower border within 7–8 cm of the anal verge. For higher cancers the mesorectum was excised to a point at least 5 cm below the tumour. Previous studies have noted retrograde mesorectal metastases[8–11]. Such deposits were normally within 2 cm, and rarely more than 5 cm, of the lower border of the tumour. This may explain why a more conservative mesorectal excision has apparently produced a similar result to that of a total mesorectal excision. The importance of other technical aspects such as high vascular ties, minimal tumour handling and the value of a rectal washout remain to be determined[12,13].

A less satisfactory result was the anastomotic leak rate. The first seven leaks in the present series occurred because the proximal colon became ischaemic. Six anastomoses were below the peritoneal reflection. The author now divides the marginal artery to ensure that there is pulsatile bleeding at the level of the anastomosis. The anastomotic leak rate has subsequently been 4 per cent. It has been suggested that mesorectal excision leaves a denuded, and hence ischaemic, rectum. This does not seem to be a universal problem[14].

In the present study local control appeared to limit the later development of distant metastases; this is in keeping with MacFarlane and colleagues' observation[3]. Also in the present study patients who developed distant metastases had an unusually large number of histological features associated with a poor prognosis and developed their metastases within 12 months. This suggests that micrometastatic dissemination had occurred before surgery[15]. It is not known whether the reduction in distant metastases occurring after 12 months was a consequence of the low local recurrence rate. If so, it would imply that many rectal cancers have not disseminated at the time of surgery. This, in turn, would suggest that metastatic disease develops in the postoperative period because foci of cancer are left and it is these that subsequently generate metastases.

In conclusion, this study supports the suggestion that mesorectal excision may reduce local recurrence; this may, in turn, improve survival[3]. Any such improvement may be of importance when assessing the value of adjuvant therapy.

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Case report

'Residual' appendicitis following incomplete laparoscopic appendicectomy

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Laparoscopic appendicectomy for appendicitis is a recent development and has recently been advocated as the preferred approach[1,2]. A case of 'residual' appendicitis following incomplete laparoscopic appendicectomy is presented.

Case report

A 25-year-old man presented with a 12-h history of central abdominal pain, nausea and anorexia in association with pyrexia (37·8°C) and leucocytosis ($18{\cdot}0 \times 10^9$/l). The patient reported that 18 months previously he had undergone laparoscopic appendicectomy for acute appendicitis in another hospital. On examination there was lower abdominal peritonitis and scarring compatible with previous laparoscopic surgery. Abdominal radiograph demonstrated the presence of two metallic clips in the right iliac fossa (*Fig. 1*). Lower midline laparotomy revealed copious purulent peritoneal fluid and an inflamed perforated retrocaecal appendix. Standard appendicectomy was performed with thorough peritoneal lavage. Pathological examination confirmed acute transmural suppuration involving a 3·2-cm appendix stump. The presence of two metallic clips within the specimen was confirmed by radiographic examination. Discharge on day 11 after operation was delayed by a chest infection and pleural effusion. Case records relating to the previous operation confirmed that he had undergone a laparoscopic appendicectomy and pathological examination had confirmed removal of an inflamed 4·5-cm appendix.

Discussion

Laparoscopic appendicectomy for acute appendicitis is increasingly popular. Controlled data suggest that it may be able to equal the excellent results and low morbidity and mortality rates of open operation. However, it is easy to imagine how the base of an acutely inflamed appendix might be obscured so that an incomplete laparoscopic appendicectomy is performed, even when the operation is undertaken, as in this case, by a consultant surgeon experienced in laparoscopy. To the authors' knowledge one other similar case has been previously reported[3]. It is not surprising that incomplete appendicectomy should be complicated by further inflammation because if the appendix is retained after a conservatively managed episode of acute appendicitis, there is a 35 per cent chance of recurrence[4]. More importantly, faced with a reliable history of previous appendicectomy, the surgeon will fail to include acute appendicitis in the differential diagnosis of acute abdominal pain, with potentially serious consequences.

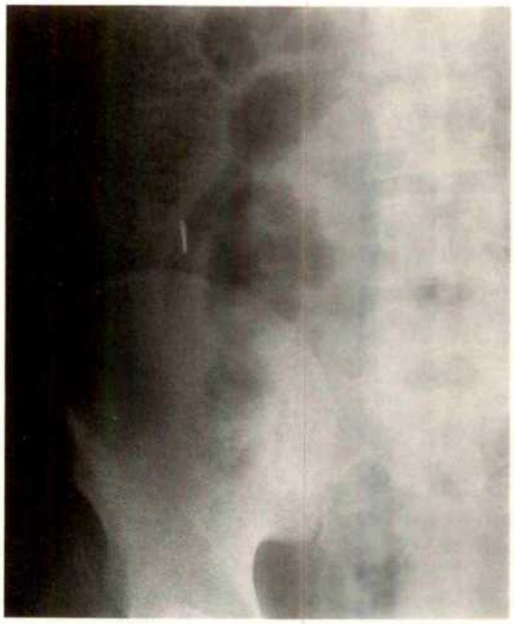

Fig. 1 Admission plain abdominal radiograph of a 25-year-old man presenting with 'residual' appendicitis showing two metallic clips placed across the midpoint of the appendix during prior incomplete laparoscopic appendicectomy for acute appendicitis

It is concluded that incomplete appendicectomy is a serious complication peculiar to the laparoscopic approach. It should be avoidable if the base of the appendix is clearly identified. Residual appendicitis should be included in the differential diagnosis of a patient presenting with convincing symptoms and signs of appendicitis and a history of previous laparoscopic appendicectomy; open surgical intervention should not be delayed.

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Incidence of third-degree perineal tears in labour and outcome after primary repair

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The incidence and outcome of third-degree tears following 16583 vaginal deliveries were prospectively assessed over a 5·5-year period. Ninety-three deliveries (0·56 per cent) were complicated by a third-degree tear and the patients underwent primary repair. Eighty-one patients were reviewed 3 months postpartum at a colorectal clinic. Third-degree tears were significantly more common in primigravidae and mothers with higher birth-weight babies. They were significantly associated with the use of forceps and were not prevented by episiotomy. Of the 81 patients reviewed, 30 had an abnormal anorectal examination. Six patients (7 per cent) were incontinent of faeces. A further ten (12 per cent) were incontinent of flatus only. The overall incidence of faecal incontinence was 0·04 per cent. An important group of women with significant subclinical sphincter injury was identified. Obstetric trauma causes significant anorectal dysfunction and patients with third-degree tears require assessment by a colorectal specialist.

Damage to the perineum is a common complication of vaginal delivery[1]. The majority of cases are first- and second-degree tears with minimal clinical sequelae. Third-degree tears occur in a significant minority of patients and, despite primary repair, are often complicated by a variable degree of anal incontinence[2,3]. Up to 40 per cent of women are incontinent following obstetric tears of the anal sphincter[4] although the majority of these women are incontinent of flatus only.

Faecal incontinence is a devastating complication of vaginal delivery yet the prevalence is unknown. This is partly due to the absence of appropriately designed prospective studies but also because the available retrospective data are clouded by the reluctance of many embarrassed patients to admit to symptoms[5]. This embarrassment is coupled with a lack of awareness, among doctors and patients alike, of the potential benefits of surgical repair. Reported series of delayed sphincter repair for faecal incontinence demonstrate that, when the condition is a result of obstetric injury, patients do well after surgery[6], particularly if it is performed early[7,8]. The aims of this prospective study were to document the incidence of third-degree perineal tears, assess the efficacy of primary repair by obstetricians, and determine the incidence of anal sphincter damage and faecal incontinence due to obstetric trauma.

Patients and methods

The work was performed over a 5·5-year period in a district maternity unit serving a population of 300000 people. All third-degree tears underwent primary repair by a member of the on-call obstetric team. A third-degree tear was defined as a laceration of the perineum involving the anal sphincter with or without involvement of the anorectal mucosa.

All patients with this tear were referred to a rectal clinic 3 months postpartum where they were assessed by one consultant colorectal surgeon (R.W.M.). Patients were questioned about continence for solid stool, liquid stool and flatus. The obstetric history was reviewed to determine parity, weight and sex of the child, the use, or not, of an episiotomy (mediolateral) and the use of obstetric forceps. Clinical examination was performed and eight clinical parameters were recorded; anterior anal sphincter length, the presence or absence of a cutaneous anal reflex, anal gape, a palpable gap in the sphincter, and the anorectal angle; resting anal pressure, voluntary squeeze pressure and cough reflex were assessed clinically on a scale of 0 (normal) to 3 (grossly abnormal) without the aid of electrophysiological measurements. The anterior sphincter length was measured by digital examination. The upper edge of the anal sphincter was palpated and the examining finger withdrawn to the lower border and then measured against a ruler.

At the end of the study, data sets were analysed by the single consultant examiner (R.W.M.). Each patient was designated as having a 'normal' or 'abnormal' sphincter mechanism based on an overall assessment of the eight recorded clinical parameters, without reference to their continence data. The overall impression was generated by attributing greatest importance to anal gape, a palpable gap in the sphincter and anterior sphincter length. Each of the pressures (resting, voluntary squeeze and cough) was equally weighted though attributed less importance. Cutaneous reflex was given least weight in the overall assessment of the sphincter and the decision to call it 'normal' or 'abnormal'.

To facilitate comparisons between patients with varying degrees of sphincter injury they were divided into three arbitrary, although clinically relevant, groups: those with a normal clinical examination (group 1); those with an abnormal clinical examination but no history of faecal incontinence (group 2); and those with an abnormal clinical examination who were incontinent of faeces (group 3). Statistical analysis of the data was performed using χ^2 and Student's t tests. Differences were considered significant at the 1 per cent level.

Results

Prevalence of third-degree perineal tear

There were 16583 vaginal deliveries during the study period. Ninety-three women (0·56 per cent) sustained a third-degree perineal tear and were referred to the colorectal follow-up clinic. Twelve women did not attend. The data presented relate to the 81 patients who did attend for follow-up.

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Women who sustained third-degree tears were predominantly primigravidae who had required an episiotomy. There was a significantly higher incidence of forceps-assisted deliveries and the mean birth weight in this group was significantly higher than in the population in general (*Table 1*).

Outcome of primary repair of third-degree tear

Anal incontinence was reported by 16 of the 81 women (20 per cent) who sustained a third-degree tear. Six were incontinent of faeces and a further ten were incontinent of flatus only. The overall incidence of faecal incontinence in 16583 vaginal deliveries was 0·04 per cent.

Women in group 1 ($n = 51$) had a normal clinical examination. Unexpectedly, this group included one patient who reported incontinence of liquid stool and four with incontinence of flatus. Women in group 2 ($n = 25$) had an abnormal clinical examination but no history of faecal incontinence. Six women in this group reported incontinence of flatus. Women in group 3 ($n = 5$) had an abnormal clinical examination and were incontinent of faeces. The overall relationship between clinical examination and anal continence is shown in *Table 2*.

Table 1 Comparison of obstetric details between women who did, and did not, sustain a third-degree tear following vaginal delivery

	Patients with third-degree tears ($n = 81$)	Total local population ($n = 16583$)	*P*
Maternal age	27·9	26·8*	—
Mean birth-weight (kg)	3·63	3·37	< 0·001
Primigravidae	64 (79)	6799 (41·0)	< 0·001
Episiotomy	60 (74)	4643 (28·0)	< 0·001
Forceps	26 (32)	829 (5·0)	< 0·001

Statistical analysis of the differences in incidence between groups was by χ^2 test while comparison of mean birth-weights was analysed by Student's *t* test. Values in parentheses are percentages. *Mean age for a subset ($n = 782$), rather than the entire study population

Table 2 Relationship between clinical examination of sphincter and continence in 81 patients following primary repair of third-degree tears

	Continence		
		Incontinent	
Clinical assessment	Continent	Faeces	Flatus
Normal	46 (90)	1 (2)	4 (8)
Abnormal	19 (63)	5 (17)	6 (20)
Total	65 (80)	6 (7)	10 (12)

Values in parentheses are percentages

Table 3 Incidence of episiotomy and forceps-assisted deliveries in women sustaining third-degree tears

	Abnormal examination and faecal incontinence ($n = 5$)	Abnormal examination without faecal incontinence ($n = 25$)	Normal examination ($n = 51$)
Episiotomy	5 (100)	15 (60)	39 (76)
Forceps	3 (60)	10 (40)	13 (25)

Values in parentheses are percentages

While episiotomy was frequently carried out in all three groups, forceps-assisted deliveries were strongly associated with the development of sphincter damage (*Table 3*). The anorectal angle was invariably normal and the data are not presented.

Discussion

The 0·56 per cent incidence of third-degree tears in this study is almost identical to that recently reported by Sultan *et al.*[9] in a study of 8603 vaginal deliveries in the UK. The risk factors for third-degree anal tears are well known[2,9]. They include primiparity, instrumental delivery, large birth-weight babies, abnormal presentation, a prolonged second stage of labour and oxytocin stimulation. While the present study confirms the increased incidence of third-degree tears in primiparae and those women having forceps-assisted deliveries, the role of episiotomy in the aetiology of these tears remains uncertain[10]. There is growing evidence that episiotomy does not always protect against tear and in some studies episiotomy has been shown to be associated with a higher incidence of tear[11]. In the present study 74 per cent of women who sustained a third-degree tear had an episiotomy compared with 28 per cent in the population overall. The episiotomy employed was mediolateral, as is commonplace in the UK. The proposed advantage of the mediolateral episiotomy over median episiotomy is that it supposedly reduces the incidence of tear[1]. In the present study confounding variables such as breech presentation or instrumental delivery prevent firm conclusions. The relationship of episiotomy to third-degree tears remains uncertain and thus awaits a randomized prospective trial[10].

Previous reports[2] have shown that these tears have a variety of long-term sequelae including perineal pain, dyspareunia and anal incontinence. Of these, faecal incontinence is a particularly devastating complication, yet its prevalence is unknown and almost certainly underestimated[5]. The symptoms may be hidden by women who either assume these symptoms to be part of their lot following childbirth or are not willing to admit to the problem. Browning and Motson[7] reported that there was a lack of awareness of the treatment of the condition, while Haadem *et al.*[3] noted that half the women in their study still had symptoms between 2 and 7 years after injury. In the present study the overall incidence of faecal incontinence was 0·04 per cent. After a third-degree tear the incidence was 7 per cent and a further 12 per cent were incontinent of flatus. It is important to note that faecal urgency was a common symptom in the latter group, many of whom were not willing to put their continence to the test.

As well as documenting the incidence of third-degree tears, a primary endpoint of this study was to assess the efficacy of primary repair after obstetric injury. The repairs were performed by the obstetric senior house officers and registrars on call, the majority of whom were unaware that any formal colorectal follow-up was being performed on these patients. The results of the primary repairs are therefore likely to be representative of the results throughout the UK.

It has been shown previously that following an uncomplicated vaginal delivery anorectal pressure profiles are reduced, but return to normal by 3 months postpartum[12]. Pressure profiles in women who sustain a third-degree tear also improve during the first 3 months postpartum but show no subsequent improvement thereafter[12]. Three months therefore seems an appropriate arbitrary interval after delivery to assess women who have sustained a third-degree tear. Physiological studies have previously demonstrated that the cause of early incontinence following obstetric injury is disruption of the external sphincter, with or without an associated pudendal nerve injury[13]. Haadem *et al.*[3] demonstrated that there is reduced external sphincter strength in most women with symptoms of anal incontinence. They pointed out that if the tear extended into the rectal mucosa there was also evidence of impaired internal sphincter function. In keeping with this a marked reduction in voluntary squeeze pressure and of resting anal tone was found as the injuries became more severe.

These findings are similar to the endosonographic findings of Burnett *et al.*[14] who demonstrated internal sphincter defects in 65 per cent of patients with anal incontinence due to obstetric trauma. In the recent study by Sultan *et al.*[9], all women with impaired continence following primary repair had sonographic defects in both internal and external sphincters while pudendal nerve motor latencies were normal in the majority of patients. It appears therefore that the severe cases of obstetric trauma associated with abnormal anal function result from a combination of external and internal sphincter injuries while pudendal neuropathy may play a minor role.

In the present study the anorectal angle, due to the puborectalis sling, was not altered and does not appear to play any role in early abnormalities of function following a third-degree tear.

Hallan *et al.*[15] have shown that digital examination by a specialist compares favourably with manometric assessment of anal sphincter function. While sophisticated techniques are not required to identify patients with faecal incontinence or those with significant sphincter injury, the value of endoanal ultrasonography and physiological testing must be emphasized if the patient is to be considered for surgical repair. Laurberg *et al.*[16] demonstrated that eight of ten patients without nerve damage had good or excellent results following repair whereas only one of nine women with proven pudendal nerve injury had a good result.

The occurrence of a third-degree tear has significant implications for obstetric management in subsequent pregnancies. Laurberg *et al.*[16] identified a subgroup of women who sustained a tear who then had a significant deterioration in anal continence after subsequent vaginal deliveries. Bek and Laurberg[17] demonstrated that transient anal incontinence after an initial third-degree tear was associated with a significantly increased risk (39 per cent) of anal incontinence after a subsequent vaginal delivery.

This study indicates that all women who sustain a third-degree tear should be followed up in a colorectal clinic. Using clinical methods alone a large number of women with significant, albeit asymptomatic, sphincter injury following third-degree tear has been identified. This subgroup may also be detected by anal endosonography after primary repair of a sphincter rupture[18]. In that study anal endosonography was significantly more sensitive than physical examination.

A subgroup of women (25 of 81; 31 per cent) who have subclinical sphincter injury has been identified. The authors agree with the hypothesis of Nielsen *et al.*[18], who attribute the continence of this group of women to their youth and inherent ability to compensate for the external sphincter defect. Some of these women may well become incontinent as they get older, particularly if they have further vaginal deliveries.

Sultan *et al.*[9] concluded that primary repair of a third-degree tear is probably inadequate in most patients. In the present prospective clinical study, 7 per cent of patients had faecal incontinence and 37 per cent had an abnormal anal sphincter 3 months after primary repair of a third-degree tear. Clearly a significant number of women receive inadequate initial treatment. This raises the question of who should be performing the primary repair. Should surgeons with expertise in anorectal surgery be involved from the outset? The authors believe that colorectal follow-up should be mandatory for all women who sustain a third-degree perineal tear during labour, regardless of who performs the primary repair. This policy will permit early identification of patients with faecal incontinence and will prevent delay in referral for operative repair. It will also identify patients who may be better advised to have an elective Caesarean section in subsequent pregnancies rather than risk developing faecal incontinence after a further vaginal delivery.

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British Journal of Surgery 1996, **83**, 222

Surgical workshop

Balloon tamponade for control of massive presacral haemorrhage

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Massive pelvic bleeding during mobilization of the distal rectum is a recognized complication[1], and can be difficult to control. A technique for dealing with this complication, involving pelvic venous tamponade with a perineal Sengstaken–Blakemore tube is described.

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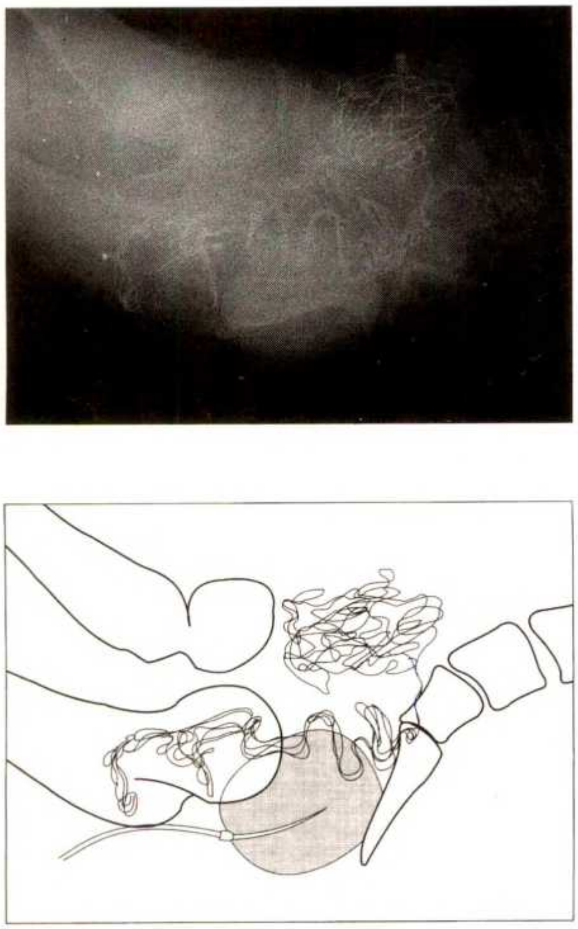

Fig. 1 Lateral pelvic radiograph showing perineal Sengstaken–Blakemore balloon overlying distal sacrum. The position of the balloon can be seen clearly in the diagram

Surgical technique

Staged proctectomy was performed in a 61-year-old woman with residual ulcerative proctitis. The rectal stump was found to be densely adherent to surrounding structures, including the posterior wall of the urinary bladder, and following excision of the rectal stump massive venous bleeding was encountered from the distal presacral area. Despite attempts at direct ligation, local haemostasis, diathermy and ligation of both internal iliac arteries, profuse haemorrhage continued (11 litres over 90 min). Gauze pads were placed over the bleeding area and a four-lumen Sengstaken–Blakemore tube was inserted through the perineal wound. The gastric balloon was inflated with air to a volume adequate for compression of the presacral region (400 ml), and distal traction was applied (*Fig. 1*). Following tamponade the subsequent blood loss measured 1·5 litres, and subsided as the severe coagulopathy improved (prothrombin time 65 s (control value 13 s), partial thromboplastin time 249 s (control value 31 s), fibrinogen 0·2).

Total blood loss was measured at 12·5 litres and intraoperative fluid replacement comprised 5·5 litres colloid, 3 litres crystalloid, 20 units concentrated red cells, 11 units fresh frozen plasma, 22 units cryoprecipitate and 16 units platelets.

The patient remained stable in the intensive therapy unit over the next 4 days without further haemorrhage. By the fifth postoperative day there was sufficient improvement in the coagulation abnormalities to enable a second laparotomy to be performed. As there was no further bleeding from the presacral area, the packs and Sengstaken–Blakemore tube were not replaced. Thereafter the patient made a steady recovery, complicated only by a small sacral pressure sore. She was discharged home 30 days after surgery.

Discussion

The combination of overlying packs and sustained balloon pressure to the distal sacrum may be the best method of controlling haemorrhage in the relatively inaccessible sacral venous sinus and lateral sacral venous tributaries[2]. The success of this technique may be related to the fact that a compressible sphere is easily accommodated in the contours of the presacral space and that it can exert a greater tamponade effect over a wider area than packing alone.

Although the coagulopathy improved in this case with the transfusion of fresh frozen plasma, cryoprecipitate and platelets, the derangement was not fully corrected. This suggests that balloon tamponade was primarily responsible for controlling the haemorrhage[3].

When confronted with this crisis during proctectomy, perineal balloon tamponade should therefore be considered as a valuable life-saving manoeuvre.

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Short note

The retrocaecal appendix appears to be less prone to infection

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Appendicectomy is the most commonly performed emergency surgical procedure. Several reports suggest that the retrocaecal position of the appendix is the commonest with an incidence between 45 and 65 per cent[1,2]. Most incidence figures are based on autopsy reports. In clinical practice the incidence is lower[3,4].

It is possible that different anatomical positions of the appendix might affect its susceptibility to acute inflammation. In this series the relationship between the position of the appendix and the presence of acute inflammation was studied.

Patients and methods

Six hundred consecutive cases of acute appendicitis admitted and operated in the years 1988–1992 were studied retrospectively. Personal, clinical and operative details were recorded. The operating surgeon noted the position of the appendix. Cases with a normal appendix were excluded from the study. Appendicitis was diagnosed and graded according to standard histological criteria. Urine microscopy was used to diagnose haematuria (more than ten red blood cells per high-power field) and pyuria (organisms seen, or more than ten white blood cells per high-power field).

Results were analysed using the χ^2 test, and $P<0{\cdot}05$ was considered to be significant.

Results

There were 382 male and 218 female patients (7:4) aged 13–69 years. The incidence of various positions of the appendix and its relation to haematuria and pyuria is shown in *Table 1*. In this series, the pelvic position (53 per cent) was the most common while a retrocaecal appendix was present in only 19 per cent of cases. The incidence of haematuria and pyuria was greater in retrocaecal appendicitis than in appendicitis in other positions ($\chi^2=16{\cdot}7$, 1 d.f., $P<0{\cdot}01$). Advanced appendicitis (perforated or gangrenous) was more common in retrocaecal appendices ($\chi^2=13{\cdot}2$, 1 d.f., $P<0{\cdot}001$). There was considerable overlap between the findings of advanced appendicitis and haematuria/pyuria: in the retrocaecal group 22 patients showed both features.

Table 1 Incidence of various positions of the appendix, and associated haematuria/pyuria and advanced appendicitis

Position of appendix	Total no.	No. with haematuria/ pyuria	No. with advanced appendicitis*
Pelvic	318 (53)	35 (11)	54 (17)
Retrocaecal	114 (19)	24 (21)	33 (29)
Paracaecal	108 (18)	4 (4)	14 (13)
Subcaecal	42 (7)	0 (0)	3 (7)
Preileal	12 (2)	0 (0)	0 (0)
Postileal	6 (1)	0 (0)	0 (0)
χ^2 (5 d.f.)		25·9	19·0
P		0·0001	0·0019

Values in parentheses are percentages. *Gangrenous or perforated appendix

Discussion

Appendicitis is a common surgical emergency. Atypical signs and symptoms are common. The diagnosis is generally based on history and physical examination, supported by haematological and radiological tests. It is thought that the different positions of the appendix might be one reason for the variety of signs and symptoms in acute appendicitis.

There are diverse reports about the position of the appendix. The reported incidence of retrocaecal appendix ranges from 20 to 65 per cent[1–4]. According to traditional teaching, which is based on autopsy reports, the retrocaecal appendix is the most common[1,2]. This finding is not confirmed in surgical practice, as also seen in the present series.

Two reasons are suggested for the discrepancy between the incidence of retrocaecal appendix in autopsy series and surgical series. First, this series shows a greater incidence of haematuria and pyuria in patients with retrocaecal appendicitis. Some early cases may have been misdiagnosed as urinary tract infection, so that the true incidence of retrocaecal appendix may be under-reported in surgical series, as patients with early (catarrhal) retrocaecal appendicitis may be treated with antibiotics after misdiagnosis. This hypothesis is consistent with the present observation of a greater incidence of advanced appendicitis in the retrocaecal position. However, the excess of advanced cases could also be explained by delay in diagnosis and operation. Unfortunately, data concerning delay were not collected in this series. The rate of normal appendicectomy for suspected appendicitis is low in this hospital, because patients tend to present late with obvious signs. This fact has prevented comparison of the position of normal and inflamed appendices.

Second, the retrocaecal position may be a beneficial one which makes the appendix less prone to infection. In the pathogenesis of acute appendicitis, obstruction is an important factor[5]. Increased intraluminal pressure is transmitted to the appendicular wall and causes ischaemia because of pressure on the intramural vessels. This ischaemia may lead to mucosal necrosis, infection and gangrene. Gravity-aided drainage of the appendicular lumen may reduce episodes of luminal obstruction and

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could explain the lower than expected incidence of retrocaecal appendicitis in this and other surgical series.

It is concluded that a retrocaecal position, in addition to making the diagnosis of appendicitis more difficult, may also protect against this condition.

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Overexpression of p53 in duodenal tumours in patients with familial adenomatous polyposis

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Duodenal polyps and tumours of different histology from patients with familial adenomatous polyposis (FAP) were examined for p53 overexpression to determine the genetic events in duodenal tumorigenesis. Samples from endoscopic biopsy specimens of 152 duodenal adenomatous polyps (taken from 79 patients) and from 13 surgically resected adenomatous polyps or cancers (taken from nine patients) were studied by routine histological examination and immunohistochemistry. p53 was overexpressed in: 0 per cent of normal mucosa samples (none of 29), 25 per cent of tubular adenomas (28 of 111), 72 per cent of tubulovillous and villous adenomas (13 of 18) and 100 per cent of duodenal cancers (seven of seven); and in 28 per cent of mildly dysplastic polyps (32 of 113), 56 per cent of moderately or severely dysplastic polyps (nine of 16) and 100 per cent of cancers (seven of seven). Overexpression of p53 increased with passage down the adenoma–carcinoma pathway and might therefore be a valuable additional marker of risk for duodenal malignancy in patients with FAP.

Patients with familial adenomatous polyposis (FAP) undergo prophylactic colectomy to forestall the development of colorectal cancer. This operation results in a considerable improvement in survival, but not to the same level as the population without FAP[1]. This failure to attain normal life expectancy is due in large part to the development of duodenal cancer in patients with FAP[2,3]. There is good evidence for the existence of the adenoma–carcinoma sequence in the duodenum of patients with FAP[4]. However, the presence of a duodenal adenoma *per se* does not equate with cancer risk, because duodenal adenomas are found in most patients with FAP, whereas only 5 per cent of them develop duodenal cancer[5].

Current methods of prediction of malignant risk rely on the severity of polyp dysplasia, the size of polyps, their degree of villous formation and induration. More accurate predictive information may be yielded by studies at the molecular level. For example, mutations of the tumour suppressor gene p53 are thought to be associated with the transformation of precancerous lesions to carcinomas in the whole gastrointestinal tract, including the oesophagus[6], stomach[7], colon[8] and pancreas[9], despite differing environmental conditions[10]. The mutant form of p53 protein has a long half-life, making abundant p53 protein that can be detected by immunohistochemistry. Immunohistochemically detectable p53 proteins broadly correspond to the mutant form of the p53 gene and not to upregulation of the wild-type form[11,12]. Overexpression of p53 has also been detected by immunohistochemistry in the entire gastrointestinal tract in cancerous as well as adenomatous cells[13–16]. There is good correlation between p53 overexpression and increasing severity of dysplasia in the colon[17,18], so that p53 overexpression might be a marker for cancer risk.

Alterations in p53 in duodenal tumours from patients with FAP were examined by immunohistochemistry to investigate the adenoma–carcinoma sequence in duodenal tumours and determine the value of p53 alterations as a marker for patients at greater risk of duodenal cancer.

Materials and methods

Materials

Endoscopic biopsy samples of 152 duodenal polyps from 79 patients with FAP were studied. Thirteen surgically resected specimens (six adenomas and seven cancers) taken from nine patients were also examined. All tissues had been processed as formalin-fixed, paraffin-embedded sections.

Immunohistochemical method

The sections were cut at 5-μm thickness and mounted on glass slides coated with 3-aminopropyltriethoxysilane[19]. Endogenous peroxidase was inhibited by adding 0·5 per cent hydrogen peroxide in methanol. The sections were then boiled in 0·01 mol/l citric acid (pH 6·0) by microwave for 30 min[20,21]. Sections were incubated with 10 per cent normal rabbit serum for 20 min before incubation with murine monoclonal antibody DO7 (NCL-p53-DO7; Novocastra Laboratories, Newcastle, UK) at a dilution of 1:100 for 45 min. Sections were incubated with biotinylated antimouse antibody at a dilution of 1:250 for 30 min and then covered with streptavidin horseradish peroxidase for 30 min. After treatment with diaminobenzidine tetrahydrochloride for 5 min the sections were lightly counterstained with Mayer's haematoxylin and with 1 per cent acid alcohol. A positive control of colonic cancer known to overexpress p53 and a negative control without the primary antibody were analysed with all specimens.

Interpretation

The sections were assessed by two investigators (H.K. and I.C.T.). A positive result was defined as diffuse staining involving more than 30 per cent of epithelial cells. p53 status was assessed for all specimens, with subgroup analysis according to architecture (normal, tubular, tubulovillous and villous, cancer), severity of dysplasia (normal, mild, moderate and severe cancer) and stage of duodenal polyposis[5], incorporating architecture, severity of dysplasia, and number and size of duodenal polyps (stage I = mild, II, III, IV = severe).

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Statistical analysis

The χ^2 test or Fisher's test was applied.

Results

The seven duodenal cancers showed intense positive staining (*Fig. 1*). Thirty-two per cent of adenomas showed positive p53 staining (*Table 1*). The frequency of positive staining increased according to the change of histological appearance from normal to malignant ($P<0{\cdot}01$, *Table 2*).

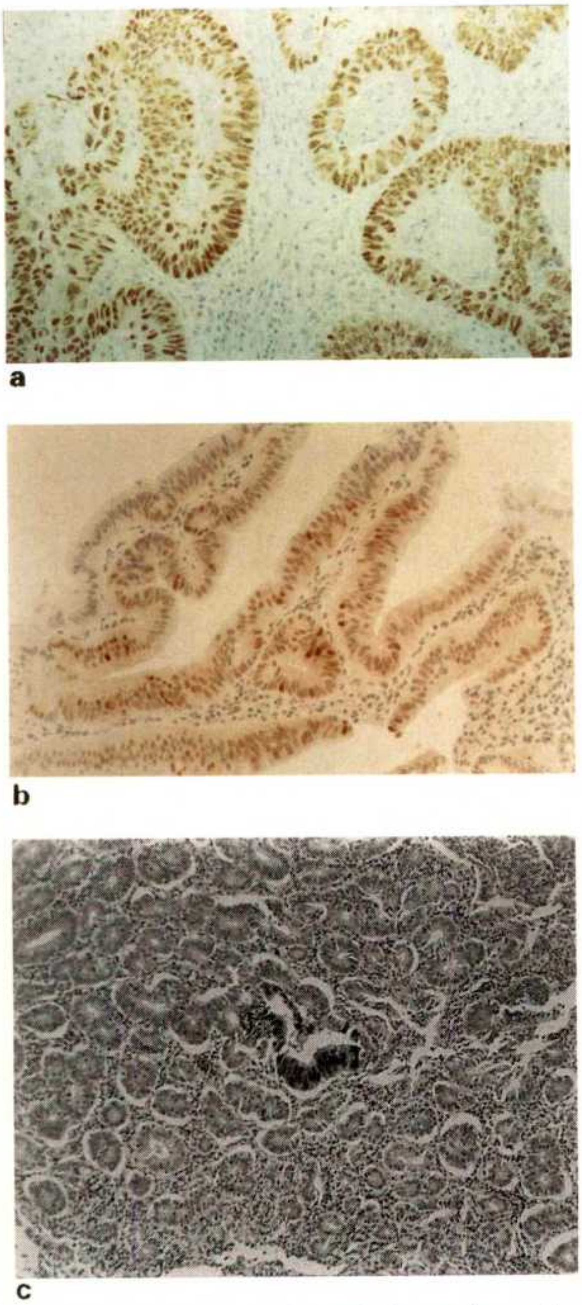

Fig. 1 p53 overexpression in **a** duodenal adenocarcinoma, **b** duodenal villous adenoma with mild dysplasia and **c** single crypt of duodenal tubular adenoma showing strong p53 overexpression. Among the adenomatous area, the sole crypt with more severe dysplasia than the surrounding adenoma shows intense positive p53 staining

Table 1 p53 overexpression in duodenal tumours in endoscopic biopsy samples from patients with familial adenomatous polyposis

	No. of samples	No. of p53-positive cases*
Normal mucosa	29	0 (0)
All adenomas	129	41 (32)
Duodenal cancer	7	7 (100)

Values in parentheses are percentages. *Frequency of staining increased according to histological appearance from normal to malignant ($P<0{\cdot}01$, χ^2 test)

Table 2 Relationship between p53 overexpression and histological and endoscopic features

	No. of samples	No. of p53-positive cases
Histological appearance		
Normal	29	0 (0)
Tubular	111	28 (25)*
Tubulovillous/villous	18	13 (72)*
Cancer	7	7 (100)
Grade of dysplasia		
Normal	29	0 (0)
Mild	113	32 (28)†
Moderate/severe	16	9 (56)†
Cancer	7	7 (100)
Stage of duodenal polyposis		
I	12	1 (8)
II	19	4 (21)
III	29	10 (34)‡
IV	12	6 (50)‡

Values in parentheses are percentages. *$P<0{\cdot}01$; †$P=0{\cdot}025$; ‡$P=0{\cdot}036$ (for stages III and IV) *versus* stages I and II (Fisher's exact test)

The frequency of positive p53 overexpression also increased according to the severity of dysplasia ($P=0{\cdot}025$, *Table 2*). In general, the staining intensity of adenomas was weaker than that of cancer, although the intensity of some adenomas was as great (*Fig. 1*). In a few adenomas, the greater the severity of dysplasia, the greater the intensity of staining. In one adenoma, the sole crypt with severe dysplasia showed intense positive staining (*Fig. 1*). Seventy-two of 79 patients were assessed for the severity of duodenal polyposis. The frequency of positive p53 staining increased according to the severity of duodenal polyposis (Stages I and II *versus* III and IV, $P=0{\cdot}036$) (*Table 2*).

Normal duodenal mucosa was uniformly negative. Staining in background stroma was not observed. No staining was noted in the negative control sections.

Discussion

In patients with FAP, p53 expression is abundant in duodenal adenomas and p53 overexpression increases with progression along the adenoma–carcinoma pathway. The present results are consistent with those found in other tumours in patients without FAP, in which p53 overexpression correlates with more advanced pathology in tumours in oral mucosa[13], oesophagus[22], stomach[15], colon[17] as well as duodenum[23]. However, the genomic site of p53 mutations in ampullary cancer in patients without

FAP differs from that found in colon cancer[23]. This finding suggests that the development of duodenal tumours might result from different stimuli to those involved in colonic tumours. An early and critical step in carcinogenesis is the formation of DNA adducts, which occurs when carcinogens bind to individual DNA bases, leading to a high risk of point mutations and activation of oncogenes or inactivation of tumour suppressor genes, such as p53. An excess of DNA adducts has been found in the duodenal mucosa of patients with FAP compared with that in controls[24]. This finding, coupled with the bile-dependent distribution of duodenal adenomas[5] and cancers[2], and the correlation between DNA adduct formation and p53 expression in rats[25], suggests that carcinogens in bile might play an important role in the genesis of p53 mutation and the subsequent development of duodenal tumours in patients with FAP.

Missense mutations of the p53 tumour suppressor gene lead to p53 protein stabilization and overexpression[11,12], but so do a host of other factors including certain DNA viruses, as well as interaction with some genes (e.g. mdm-2 or GADD45)[26,27]. Non-mutant p53 overexpression is also detected in response to ultraviolet irradiation[28], γ irradiation[29] and DNA-damaging agents[30]. Moreover, p53 overexpression may be found in normal cells in patients with family cancer syndrome, by an immunohistochemical method[31]. The detection of p53 overexpression in the absence of p53 mutation might reflect the presence of an abnormal cellular environment, which leads to p53 dysfunction and transformation of normal cells to neoplastic cells[32].

The findings of the present study indicate that p53 overexpression might be of use as an additional marker of risk for duodenal malignancy in patients with FAP. It may help in identifying those who need closer scrutiny. Evaluation of this awaits the outcome of long-term studies of those who are p53 'positive' and p53 'negative'.

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Case report

Sisters with familial adenomatous polyposis affected with thyroid carcinoma, desmoid tumour and duodenal polyposis

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After prophylactic surgery for colonic polyposis, upper gastrointestinal cancer and desmoid tumour are the main causes of death in patients with familial adenomatous polyposis (FAP). Two sisters with FAP who developed multicentric carcinoma of the thyroid, desmoid tumour and duodenal polyposis are presented.

Case reports

Patient 1

A 16-year-old Japanese girl presented with goitre, which was shown to contain multicentric papillary carcinoma of the thyroid. She underwent total thyroidectomy. Five years later, she developed melaena. FAP (with rectal carcinoma) was diagnosed, and restorative proctocolectomy performed. Duodenoscopy revealed that the patient had severe duodenal polyposis (Spigelman stage IV)[1]. She had an operation for a mesenteric desmoid tumour of the ileum at the age of 23 years.

Patient 2

Familial surveillance revealed that the younger sister of patient 1 had multiple tumours of the thyroid gland. She underwent total thyroidectomy for multicentric papillary carcinoma of the thyroid when aged 12 years, and prophylactic total colectomy and ileorectal anastomosis for colonic polyposis was carried out at the age of 15 years. This patient also has duodenal adenomas and a desmoid tumour.

Both sisters have congenital hypertrophy of the retinal pigment epithelium. *APC* gene mutation was detected by the method reported previously[2], and the germ-line mutation of the *APC* gene in both patients was AAA→TAA of codon 848 in exon 15.

Discussion

Although more than 90 per cent of patients with FAP are affected with duodenal polyposis, just 10 per cent develop advanced duodenal polyposis; severe duodenal polyposis usually occurs in older patients[1]. The older sister in the present study, however, has been affected with severe duodenal polyposis (Spigelman stage IV) from the age of 21 years. As ampullary adenoma with advanced pathology is likely to be at greater risk of early progression, effective treatment is needed[3].

Although thyroid carcinoma may occur more frequently in patients with FAP than in the general population[4], the development of papillary thyroid carcinoma in siblings is not common since familial clustering has been found in only three families with FAP[5–7]. The relatives of patients with familial papillary carcinoma of the thyroid are supposed to be at a greater risk of colonic carcinoma[8]. It might therefore be suggested that a wider genetic link exists between thyroid and colonic carcinoma. The existence of a correlation between the mutation site in the *APC* gene and the severity of the phenotype of this disease remains to be proven[9]. The sisters presented in this report might be of severe phenotype as they were affected with several manifestations of the other organs at a young age. Interestingly, the mutation locus in the *APC* gene in this family occurred at a rare site[10].

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Short note

Vitamin D_3 analogue (EB 1089) inhibits *in vitro* cellular proliferation of human colon cancer cells

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The active form of vitamin D_3, namely 1,25-dihydroxyvitamin D_3, has been shown to inhibit the proliferation of some tumour cells[1]. The use of vitamin D_3 as an antiproliferative agent in the treatment of cancer is limited, however, by its hypercalcaemic effects. Synthetic analogues of vitamin D_3 have been developed which retain cellular differentiation and growth inhibitory activities but with reduced calcaemic activity. Recently, several analogues of 1,25-dihydroxyvitamin D_3 have been shown to be potent antiproliferative agents in colon cancer cells[2]. The effects of the vitamin D_3 analogue EB 1089 in three previously untested colon cancer cell lines are reported here.

Materials and methods

Three human colonic adenocarcinoma cancer cell lines were studied. C170 and LoVo were gifts from CRC Laboratories, Nottingham, UK and LIM 1215 was a gift from the Ludwig Institute, Melbourne, Australia. Cell lines were grown as monolayers in Roswell Park Memorial Institute (RPMI) 1640 medium and 10 per cent fetal calf serum (FCS) (Gibco, Sydney, Australia) at 37°C in 5 per cent carbon dioxide.

EB 1089 was from Leo Pharmaceutical Products, Denmark, growth supplement GMS-A from Gibco and [^{3}H]-methylthymidine from Dupont, Boston, Massachusetts, USA.

Some 10^4 cells per well were plated in 24-well tissue culture plates (Costar, Sydney, Australia) in RPMI 1640 medium containing 10 per cent FCS and glutamine (2 mmol/l) and incubated for 24 h at 37°C in a humidified 5 per cent carbon dioxide atmosphere. The same batch of FCS was used throughout. After 24 h the medium was replaced with RPMI 1640 medium containing 1 per cent FCS, 1 per cent GMS-A and vitamin D_3 analogue EB 1089 (10^{-8}–10^{-11} mol/l). Control cultures containing ethanol vehicle (0·1 per cent) were incubated in parallel. Cells were cultured for up to 8 days and the medium changed on alternate days. Viability was assessed by trypan blue exclusion and proliferation was measured by [^{3}H] thymidine incorporation 4 or 8 days after addition of EB 1089 by incubation with 1 μCi per well [^{3}H] thymidine for the last 4 h of culture. The cells were precipitated with 5 per cent trichloroacetic acid and radioactivity in precipitable material determined in a β scintillation counter. Concentrations were tested in triplicate and experiments performed at least twice.

Data are reported as mean(s.e.m.) as a percentage of controls. Statistical analysis was performed using Student's t test.

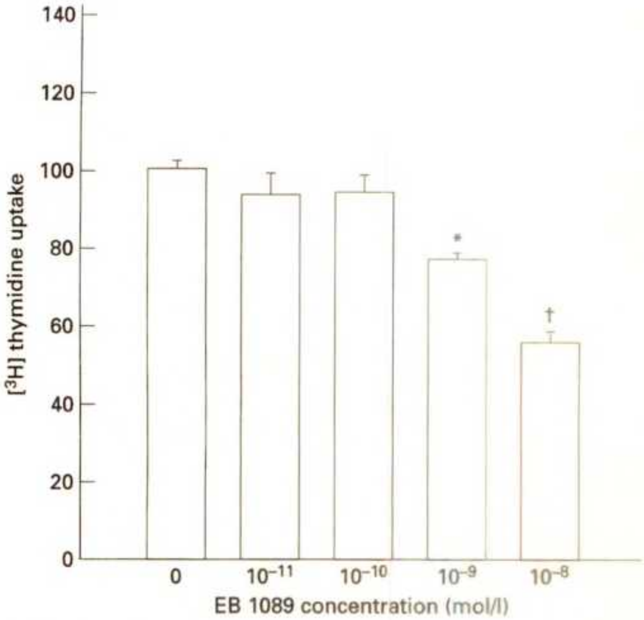

Fig. 1 Antiproliferative effects as assessed by [^{3}H] thymidine incorporation of vitamin D_3 analogue EB 1089 on LoVo cancer cells after 4 days in culture in the presence or absence of increasing amounts of EB 1089. Results are percentage of control (s.e.m.) of three replicates and representative of two separate experiments. *$t = 7{\cdot}54$, 4 d.f., $P = 0{\cdot}0017$; †$t = 12{\cdot}55$, 4 d.f., $P = 0{\cdot}0002$

Results

Significant dose-dependent inhibition of cell growth was seen with LoVo cells after 4 and 8 days of treatment with EB 1089 (*Fig. 1*). Maximum inhibition was observed at 10^{-8} mol/l (56 (2·8) per cent of control, $P < 0{\cdot}0002$) on day 4. Proliferation of cells C170 and LIM 1215 was unaffected by the vitamin D_3 analogue (data not shown).

Discussion

The vitamin D_3 analogue EB 1089 had a profound inhibitory effect on the proliferation of one of three human colon cancer cell lines. Others have reported that inhibition of proliferation by vitamin D_3 and its analogues is related to the levels of receptor expressed on the cells[2,3]. This might explain differences between cell lines. Analogues other than EB 1089 also have a significant inhibitory effect on human colonic cancer cells[4] and at a similar concentration to that used in the present study.

Vitamin D_3 and its metabolites have been shown to inhibit proliferation in normal and premalignant rectal epithelium; furthermore, calcipotriol, a vitamin D_3 analogue, inhibited the growth of HT-29 colon cancer growth in a dose-dependent manner[5].

The present findings support the belief that vitamin D_3 analogues may be useful in the clinical management of some colorectal cancers and justify further investigation.

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Non-invasive assessment of arterial disease: a comparison of Quickscan with intra-arterial digital subtraction angiography

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The ability of Quickscan to identify haemodynamically significant lesions in the arteries of the lower limb was studied. Quickscan was prospectively compared with intra-arterial digital subtraction angiography (IADSA) of the iliac, femoral and popliteal arteries. In 155 patients, 631 arterial segments were evaluated. A Quickscan frequency ratio of 1:3 or greater had a sensitivity of 93 per cent and a specificity of 85 per cent in detecting a stenosis of more than 50 per cent diameter reduction (67 per cent area reduction) in the iliac artery, as shown on IADSA. The sensitivity and specificity in the femoral artery were 85 and 96 per cent respectively, and in the popliteal artery 82 and 98 per cent respectively. In the detection of occlusion, Quickscan had a sensitivity and specificity of 84 and 98 per cent respectively in the iliac artery, 94 and 97 per cent respectively in the femoral artery, and 94 and 85 per cent respectively in the popliteal artery. Quickscan is an inexpensive, quick and non-invasive method of screening for peripheral vascular disease in the lower limb.

The purpose of diagnostic imaging in the assessment of peripheral vascular disease is to evaluate the locality and extent of the disease, and to determine the most appropriate approach to revascularization of the area of ischaemia. Currently intra-arterial digital subtraction angiography (IADSA) is recognized in many hospitals as the 'gold standard' in the quantification of arterial disease. IADSA is still commonly regarded as an essential procedure before percutaneous transluminal angioplasty or surgery. However, it is expensive, invasive and associated with a low but constant complication rate. These factors make angiography unsuitable as a routine screening method for lower-limb ischaemia. Duplex ultrasonographic scanning is becoming increasingly important in the diagnosis and follow-up of peripheral arterial disease, and has become established as the non-invasive method of choice. The findings from duplex ultrasonography have been shown to correlate well with the results of angiography[1–3]. The cost of the machine, time required to assess the major vessels in the lower limbs and requirement for an experienced ultrasonographer may limit its use in many district general hospitals. An ideal routine method for assessing patients with lower-limb ischaemia should be non-invasive, inexpensive and rapid.

Preliminary reports of the value of Quickscan before angiography in peripheral vascular disease have been published previously[4,5]. The results were similar to those of comparable duplex ultrasonography studies. In this prospective study, Quickscan was compared with IADSA to assess its usefulness in the detection of significant peripheral vascular lesions.

Patients and methods

A total of 155 patients, 64 women and 91 men, of median age 68 (range 36–89) years was studied between 1991 and 1993. All had clinically suspected peripheral vascular disease and Quickscan was performed at a median of 34 (range 1–180) days before IADSA. Arterial segments were divided into iliac, femoral and popliteal, allowing the assessment of six segments per patient. Each segment was graded into one of three categories: normal, significant stenosis or occlusion.

The theory and principles of Quickscan have been reported previously in detail[4,5]. A new portable Quickscan system (Lateral UK, London, UK) was used in this study. The operator moves a 4-MHz continuous wave Doppler pencil probe at approximately 1-cm increments along the expected path of the artery, maximizing signal strength using small lateral movements of the probe. The operator records the integer value of the peak systolic frequency from a calibrated real time display by pressing a simple button. These data are recorded by computer, together with the current position of the Doppler probe. Stenoses are heralded by a localized threefold or greater increase in peak systolic frequency. When the scan is complete, the data are replotted as a track, superimposed on a grey scale image of the patient. The tracks are colour coded with respect to the computed value of frequency ratio used to reconstruct them. Normal arteries are shown in red, stenoses with frequency ratios of 1:3 or greater are shown as a yellow mark superimposed on the red lumen. A frequency ratio of 1:3 is theoretically equivalent to a 67 per cent cross-sectional area reduction and a 1:16 ratio indicates a 94 per cent cross-sectional area reduction. The width of the yellow mark is proportional to the frequency ratio; the maximum permissible value of 1:16 almost fills the lumen. An occlusion completely overwrites the lumen in yellow (*Fig. 1*). This is recognized by the absence of arterial signal in an area where the associated vein can be heard, or by the presence of alternating retrograde and antegrade flow patterns on the spectral display, indicating the presence of collateral vessels. The final report contains patient details, scan image, stenosis severity (frequency ratio) and calf/brachial indices.

IADSA was performed in all patients. The radiologist had knowledge of the Quickscan result so that biplanar and triplanar views could be taken of arterial segments where Quickscan had indicated disease. Likewise, further views were taken of areas of disease detected by angiography. The agreement between Quickscan and angiography was assessed continuously by a vascular surgeon and a radiologist at a weekly review meeting. Results were tabulated and analysed using two-way contingency tables and the κ statistic was calculated. Sensitivity, specificity and accuracy were also calculated for normal, stenosis and occlusion of each arterial segment.

Results

A total of 631 arterial segments from a possible 930 segments in 155 patients was examined by Quickscan and

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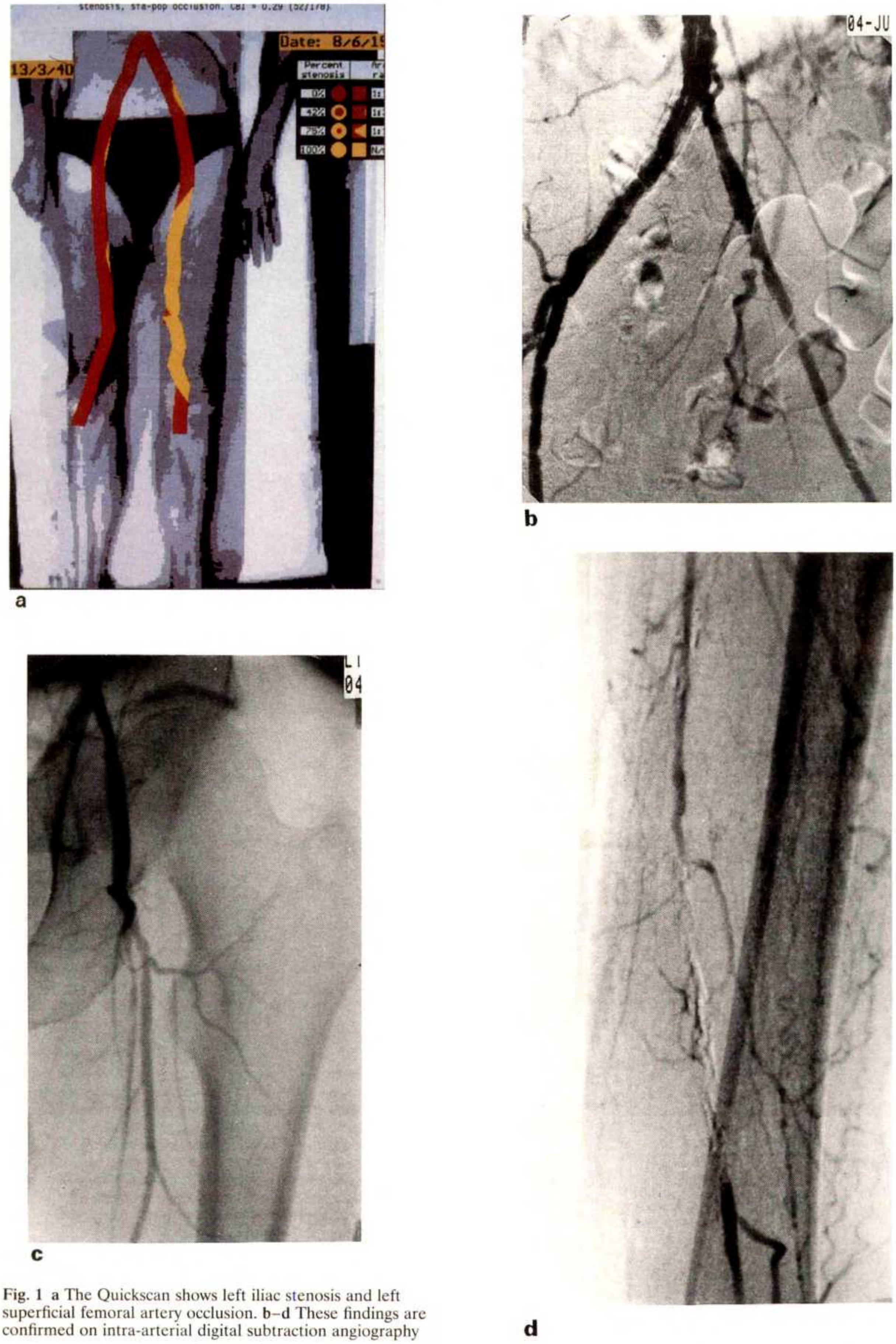

Fig. 1 **a** The Quickscan shows left iliac stenosis and left superficial femoral artery occlusion. **b–d** These findings are confirmed on intra-arterial digital subtraction angiography

Table 1 Correlation of angiography and Quickscan for each arterial segment

Quickscan	Angiography Normal	 Stenosis	 Occlusion
Iliac segment			
Normal	102	4	2
Stenosis	20	94	4
Occlusion	1	3	32
Femoral segment			
Normal	87	7	2
Stenosis	3	52	4
Occlusion	2	2	88
Popliteal segment			
Normal	79	1	0
Stenosis	1	9	1
Occlusion	15	1	15
All segments			
Normal	268	12	4
Stenosis	24	155	9
Occlusion	18	6	135

Table 2 Results of Quickscan compared with angiography as the 'gold standard'

Arterial segment	*n*	κ	Sensitivity (%)	Specificity (%)	Accuracy (%)
Iliac	262	0·79			
Normal			83	96	90
Stenosis			93	85	88
Occlusion			84	98	96
Femoral	247	0·87			
Normal			95	94	94
Stenosis			85	96	94
Occlusion			94	97	96
Popliteal	122	0·65			
Normal			83	96	86
Stenosis			82	98	97
Occlusion			94	85	86
All segments	631	0·82			
Normal			86	95	91
Stenosis			90	93	92
Occlusion			91	95	94

IADSA. This discrepancy occurred because unilateral angiography was performed in 40 patients. *Table 1* is a two-way contingency table for classification of disease by Quickscan and IADSA. Using IADSA as the gold standard, Quickscan misdiagnosed six of 38 occlusions, seven of 101 stenoses, and 21 of 123 normal lumina in the iliac segment. In 247 femoral arteries Quickscan misdiagnosed six of 94 occlusions, nine of 61 stenoses and five of 92 normal vessels. In 122 popliteal arteries Quickscan misdiagnosed one of 16 occlusions, two of 11 stenoses and 16 of 95 normal vessels. The sensitivities, specificities, accuracy and κ values for the various arterial segments are shown in *Table 2*.

Discussion

The role of angiography in the investigation of lower-limb arterial disease is rapidly diminishing as other non-invasive techniques prove their worth. Duplex scanning is a powerful non-invasive means of detecting arterial disease which can provide both anatomical and haemodynamic information. Duplex ultrasonography has been shown to correlate well with angiography but the machine is expensive, and the operator requires expertise and training. In many centres where duplex ultrasonography has become established, the demand for scans frequently exceeds the resources available.

Quickscan can assess the vascular tree from the aorta to the crural vessels and can distinguish normal artery from stenosed or occluded vessels. The procedure takes 15–20 min for a bilateral assessment to popliteal level, providing an instantaneous graphic image with calf:brachial index and a computer-generated report. An extra 10 min is required to assess the crural vessels bilaterally to the ankle. The new portable Quickscan unit can be taken to the outpatient department, avoiding the requirement for the patient to make multiple visits to different parts of the hospital. Examination of the popliteal artery in the supine position is difficult and time consuming, and this has been abandoned in favour of scanning the patient in the prone position. The computer makes the necessary transposition required to display the complete scan as an anteroposterior view. If the Quickscan detects no disease, patients can be reassured that there is nothing wrong with their arteries and this can be visually reinforced by the computer graphic. Stenoses and occlusions can be detected, and further investigation or treatment may be planned on the result of the scan.

The Quickscan uses a continuous wave Doppler signal. The main advantage of this is that vessels which are difficult to find on duplex scanning are more readily identified with Quickscan. The superficial femoral artery in the adductor canal and crural vessels are notoriously difficult to assess with the pulsed Doppler of duplex scanning, yet these are detected easily with Quickscan. The main drawback of Quickscan is the lack of anatomical information, for example a large collateral vessel overlying an occlusion may be misinterpreted by this method. Likewise, Quickscan cannot give any useful information about the length of an occlusion or stenosis, but the identification of an area of disease allows the duplex scanner to be used more efficiently.

Duplex scanning of the iliac arteries is difficult in obese patients and bowel gas can preclude good visualization of the vessels. Quickscan has a 98 per cent success rate in scanning the iliac segment without the need for fasting; this compares with a success rate of around 90 per cent using duplex scanning with the patient fasted. This is a major advantage of Quickscan over duplex scanning and is in part due to the smaller acoustic window required by the Quickscan pencil probe. Legemate *et al.*[6] have reported a sensitivity of 92 per cent and specificity of 98 per cent for the detection of a significant iliac stenosis (more than 50 per cent diameter reduction) on duplex scanning. Moneta *et al.*[3], in a study of 79 patients, reported a sensitivity of 88 per cent and a specificity of 97 per cent. Quickscan results are comparable, with a sensitivity of 93 per cent and a specificity of 85 per cent for stenosis, and 84 per cent and 98 per cent respectively for occlusion. Quickscan in the femoral arteries is also comparable in results to duplex scanning, with sensitivity and specificity of 85 and 96 per cent respectively for stenosis, and 94 and 97 per cent respectively for occlusion[6,7]. The popliteal arteries were scanned in the prone position and the results were 82 per cent sensitivity and 98 per cent specificity for stenosis, and 94 per cent sensitivity and 85 per cent specificity for occlusion. The results are less satisfactory in the popliteal artery than in the femoral and iliac arteries;

this reflects the general difficulties of non-invasive imaging of the popliteal artery. The overall Quickscan results of 90 per cent sensitivity and 93 per cent specificity in the detection of significant stenosis, and 91 per cent sensitivity and 95 per cent specificity for occlusion are also similar to recent results of duplex scanning[3]. A normal Quickscan assessment virtually excludes significant disease (negative predictive value 94 per cent).

In conclusion, Quickscan can provide an inexpensive, quick and non-invasive screening for routine assessment of peripheral vascular disease and help avoid unnecessary angiography. Although it is not as accurate as duplex scanning, Quickscan may have a role in hospitals where duplex scanning is not available. It may also be used as a screening method to save valuable duplex scanning time.

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Announcement

The Rouleaux Club

The Rouleaux Club is a society for surgical trainees who have an interest in vascular surgery. The club meets twice a year, once for a weekend meeting in summer and once at the Vascular Surgical Society in November.

The club provides a social setting where members meet and find mutual support especially in areas related to vascular research. The club is increasingly seen as the mouthpiece of vascular trainees and as such we wish to ensure that all trainees with a vascular interest have the opportunity to join.

All surgical registrars, research fellows or senior registrars with an interest in vascular surgery are invited to join the Rouleaux Club. Membership is free.

Please address all enquiries to: Mr Mark Whiteley, Secretary, The Rouleaux Club, Department of Surgery, Royal Berkshire Hospital, London Road, Reading RG1 5AN, UK. (From 1 April 1996: Nuffield Department of Surgery, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK).

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Mid-aortic syndrome presenting in childhood

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Mid-aortic syndrome (MAS) is an uncommon condition characterized by segmental narrowing of the proximal abdominal aorta and ostial stenosis of its major branches. It is usually diagnosed in young adults, but may present in childhood as a challenging problem. Over the past 20 years 13 patients with MAS have presented to this institution. All had hypertension, four had associated neurofibromatosis, three persistent eosinophilia and three had Williams syndrome. In all cases arteriography showed a smooth segmental narrowing of the abdominal aorta with concomitant stenosis at the origins of the renal arteries. Six children were successfully treated with antihypertensive medication alone. Percutaneous transluminal angioplasty was attempted in two cases with poor result. Surgery was indicated in seven children with refractory hypertension and progressive renal impairment. Techniques used to revascularize the kidneys included thoracoabdominal to infrarenal aortic bypass with renal artery reimplantation, splenorenal bypass, gastroduodenal to renal bypass, aortorenal bypass and autotransplantation.

Mid-aortic syndrome (MAS) is an uncommon condition found in children and young adults. The term refers to isolated disease of the abdominal aorta, comprising a severe, distinct, tubular narrowing of its proximal part with stenosis of the renal and visceral branches, a condition which usually presents with renovascular hypertension. Several reports have been published regarding its characteristics, clinical features, angiographic findings and management[1–9]. Many terms have been used to describe this condition including coarctation, hypoplasia, mesenchymal disease in neurofibromatosis and aortoarteritis. This multiplicity of terms has led to a certain amount of confusion. The term MAS is a clinicoanatomical definition, while the other terms make reference to the aetiology or pathogenesis of the disease.

This report describes 13 cases of MAS treated in Guy's Hospital during the past 20 years and presents a critical review of the literature. In this series MAS was defined by the angiographic appearance of a tubular stenosis of the abdominal aorta in the absence of any clinical or biochemical evidence of arteritis. Patients with fever, rash, arthritis, myalgia and elevated erythrocyte sedimentation rate (ESR) who had aortic narrowing associated with calcium deposits were diagnosed as having aortoarteritis (Takayasu's disease) and were excluded.

Patients

Demographic details

Of the 13 patients included in this report (*Table 1*) five were girls and eight were boys. The age at diagnosis varied from 2 months to 14 years (mean 7·1 years). Five patients were white, four black and four Asian. There was no relevant family history.

Presentation

All 13 children were hypertensive, but eight were diagnosed incidentally at routine medical examination. The diastolic blood pressure ranged from 80 to 150 mmHg. Symptomatic children presented with a combination of epistaxis, chest pain, headaches, heart failure, polydipsia, vomiting, and oedema due to renal impairment. Clinical examination demonstrated weak or absent femoral pulses in five patients, an ejection systolic murmur at the left sternal border in seven, abdominal bruit in nine and hypertensive retinopathy in three. Renal function was abnormal in eight children. All patients had a normal ESR and tested negative for antinuclear antibodies.

Associated findings

Neurofibromatosis was proved by biopsy in four cases and confirmed in two of these by genetic analysis. Three children presented with persistent eosinophilia and three had Williams syndrome. The latter is a congenital syndrome which occurs sporadically, in which hypercalcaemia is associated with developmental delay, elfin facies, anteverted nostrils, strabismus, dental anomalies, small nails, supravalvular aortic stenosis and short stature.

Radiological findings

Percutaneous transfemoral aortography was performed in all patients (*Table 2*). Oblique views were obtained as necessary to demonstrate the origins of the renal and visceral vessels (*Fig. 1a*). All patients had a smooth, segmental, tubular narrowing of the visceral aorta over a variable distance. This segment always involved the origin of the renal arteries (inter-renal stenosis) and was in continuity with ostial stenoses of either the renal, coeliac axis or superior mesenteric arteries (SMAs) in all cases (*Table 2*). Ten children had multiple renal arteries. Fifty-five renal arteries were identified in the 13 patients and of these 43 (78 per cent) had ostial stenoses. The coeliac axis was involved in eight and the SMA in nine patients. The inferior mesenteric artery (IMA) was never stenosed, but was grossly enlarged in eight patients as a wandering artery of Drummond (*Fig. 1b*). Three patients were studied angiographically more than once during follow-up. There was no progression of occlusive disease in two patients after 14 years (patient 8, *Fig. 2*) and 6 years (patient 2). However, the third developed a severe stenosis at the origin of the coeliac axis at 6 months (patient 4, *Fig. 3*).

Results

Medical treatment

Antihypertensive treatment required a combination of up to six antihypertensive drugs and achieved moderate to good control of blood pressure in all patients initially. However, control of the blood pressure was difficult to maintain and was associated with deterioration in renal function. The antihypertensive regimen varied during the

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Table 1 Clinical details of patients with mid-aortic syndrome

Patient no.	Age at diagnosis (years)	Sex	Race	Associated findings	Treatment		Follow-up (years)	Outcome
					Medical	Surgical		
1	0·2	F	Asian	Multiple congenital anomalies Development delay	Medical	—	1·1	Normotensive
2	1·3	M	White	Eosinophilia	Medical	—	2·0	Blood pressure controlled
3	2·8	F	Black	Neurofibromatosis L thigh congenital arteriovenous malformation	—	L renal reconstruction and implantation to the aorta over a PTFE aortic patch L nephrectomy	0·8	Normotensive
4	4·8	M	Black	Neurofibromatosis	—	L splenorenal/patch/nephrectomy R gastroduodenal to renal bypass, vein graft R aortorenal PTFE graft Thoracoabdominal aortic bypass, 14-mm Dacron graft	0·3	Normotensive
5	11·0	M	Black	Neurofibromatosis	—	Renal angioplasty with poor result Bilateral saphenous grafts R nephrectomy (3 years) L anastomosis angioplasty	6·0	Normotensive
6	6·3	F	Arabian	Neurofibromatosis	Medical	—	0·6	Lost to follow-up
7	6·8	F	White			Thoracoabdominal aortic graft Bilateral autotransplantation of both kidneys to the iliac vessels	1·8	Normotensive
8	6·8	M	White	Eosinophilia	Medical (15 years)	Thoracoabdominal aortic bypass, with L renal reconstruction; implantation of two renal arteries and coeliac axis into graft	15·4	Easily controlled
9	6·9	F	Black			R renal angioplasty then nephrectomy L autotransplantation (iliac vessels)	2·3	Easily controlled
10	11·1	M	White	Williams syndrome Eosinophilia	Medical	—	1·5	Blood pressure borderline
11	12·4	M	Asian	Williams syndrome		L renal autotransplantation R iliorenal vein graft	—	Died (day 5 after surgery)
12	13·8	M	Asian		Medical	—	3·2	Blood pressure controlled
13	14·2	M	White	Williams syndrome Developmental delay	Medical	—	0·2	Lost to follow-up

PTFE, polytetrafluoroethylene; L, left; R, right

course of the study, but diuretics were usually the first line of treatment, followed by β-adrenergic blockers, vasodilators and, finally, angiotensin converting enzyme inhibitors. Renal function was monitored constantly during follow-up and a raised serum creatinine level and decrease in glomerular filtration rate were not uncommon. These findings were probably due to persistent renal hypoperfusion from a combination of arterial stenosis and hypotensive medication. Of the six patients treated medically, two became normotensive with normal renal function, two were considered too young for surgery (under 2 years old) and two had acceptable control of hypertension.

Percutaneous transluminal angioplasty

Percutaneous transluminal angioplasty (PTA) was attempted in two patients. Patient 9 had a right renal angioplasty combined with autotransplantation of the left kidney. Despite initial success, the right renal artery occluded within 1 week, resulting in nephrectomy. Bilateral renal angioplasty was attempted on two occasions in patient 5, but the stenoses proved resistant to dilatation, with minimal angiographic and clinical improvement.

Surgical treatment

Seven children underwent surgery for uncontrollable hypertension, progressive renal impairment and/or complications of malignant hypertension. They are discussed below in detail (*Table 1*).

Patient 3. Left renal artery reconstruction and reimplantation to a 6-cm elliptical polytetrafluoroethylene (PTFE) aortic patch (Impra, Droitwich, UK) was attempted, but this was not successful and resulted in nephrectomy. At 1 year the child is normotensive.

Patient 4. An end-to-end splenorenal anastomosis was performed after joining the two stenosed upper pole left renal arteries together in a common ostium. The three renal arteries on the right were divided and anastomosed to the gastroduodenal artery using a reversed long

Table 2 Angiographic findings

Patient no.	Extent of disease	Renal arteries	Coeliac axis	Superior mesenteric artery	Inferior mesenteric artery	Repeat study
1	Diaphragm to infrarenal aorta	Bilateral ostial stenosis	Stenosed	Narrowed	Not seen	
2	SMA to renal arteries	Two R, both stenosed	Normal	Normal	Normal	No change
3	SMA to renal arteries	Two R, normal Two L, one stenosed	Normal	Normal	Normal	
4	Coeliac axis to renal arteries	Four L, stenosed Three R, stenosed Mid-vessel stenoses	Stenosed	Stenosed	Enlarged	Progressed
5	Diaphragm to renal arteries	Two L, one stenosed One R, stenosed	Stenosed	Stenosed	Enlarged	
6	Coeliac axis to renal arteries	Three R, two stenosed Two L, upper stenosed	Normal	Stenosed	Enlarged	
7	Diaphragm to SMA	Stenosed	Occluded	Occluded	Enlarged	
8	Coeliac axis to renal arteries	Three L, two stenosed	Stenosed	Stenosed	Enlarged	No change
9	Coeliac axis to renal arteries	Two L, stenosed	Stenosed	Stenosed	Enlarged	
10	Diaphragm to infrarenal aorta	Bilateral ostial stenosis	Normal	Normal	Normal	
11	Coeliac axis to infrarenal aorta	Orifice stenosis	Stenosed	Stenosed	Enlarged	
12	SMA to renal arteries	Two R, both narrowed Two L, one occluded, one normal Intrarenal stenoses	Occluded	Occluded	Enlarged	
13	SMA to infrarenal aorta	Two R, one stenosed Two L, one stenosed	Normal	Normal	Normal	

R, right; L, left; SMA, superior mesenteric artery

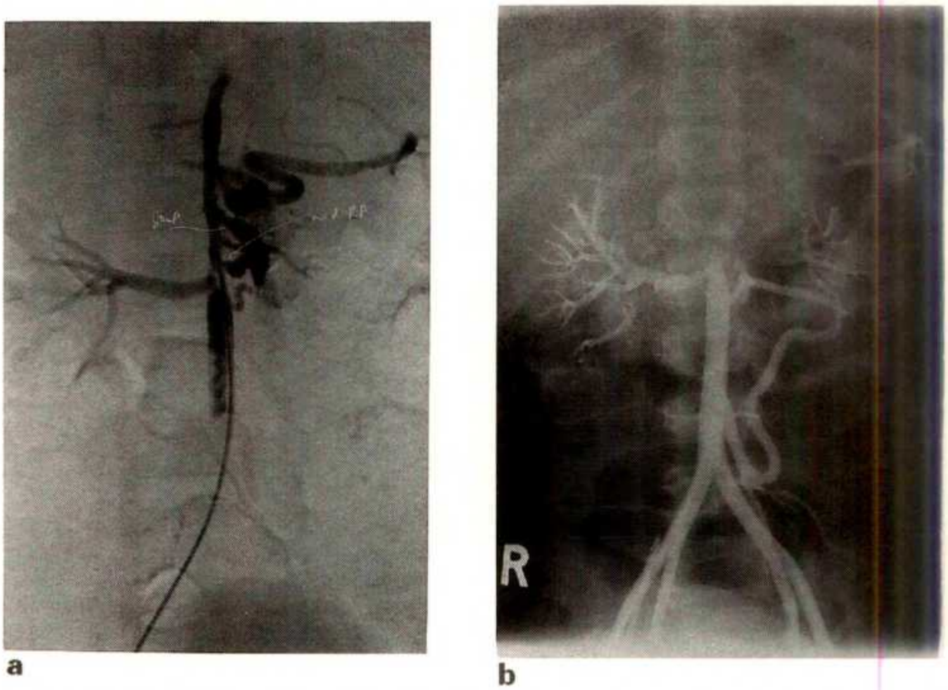

Fig. 1 Angiograms of patient 8 in 1979. **a** Lateral view showing the stenotic origin of the coeliac axis, superior mesenteric artery (with poststenotic dilatation) and the three right renal arteries; the left renal artery is not stenosed. **b** Smooth tapering of the infrarenal aorta and grossly enlarged artery of Drummond (inferior mesenteric artery)

saphenous vein graft (*Fig. 3b*). Immediately after operation the blood pressure returned to normal but acute thrombocytosis developed as a result of splenic ischaemia. This resulted in a tight stenosis proximal to the splenorenal anastomosis (*Fig. 3b*) which was patched, but satisfactory renal perfusion was never established and left nephrectomy was performed on day 10. Repeat angiography at 3 months for recurrent hypertension

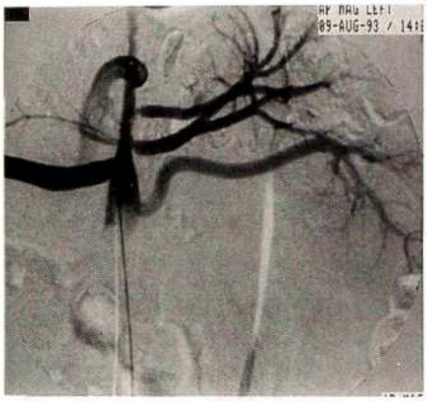

Fig. 2 Angiogram of patient 8 in 1993. The lesions are still the same 14 years later (see *Fig. 1*)

showed an ostial stenosis of the coeliac axis and aneurysmal dilatation of the vein graft had occurred. This was replaced with a PTFE graft (Impra) to the infrarenal aorta. However, the inflow was poor and a 14-mm polyester (Dacron) graft (Meadox, Caddington, UK) was inserted between the supracoeliac and infrarenal aorta, using medial visceral rotation for exposure. At 3 months the child is normotensive.

Patient 5. Bilateral renal artery angioplasty was unsuccessful and saphenous vein grafts were inserted from the infrarenal aorta to both renal arteries. The right graft occluded and nephrectomy was performed. Some 4 years later a severe stenosis developed at the left renal anastomosis which was angioplastied with good radiological and clinical results. At 6 years the blood pressure is easily controlled with diuretics.

Patient 7. A bypass from the supracoeliac to the infrarenal aorta was performed via a thoracoabdominal approach using medial visceral rotation. Both kidneys were autotransplanted to the iliac vessels. At 18 months the child is normotensive.

Patient 8. After being treated medically for 15 years, surgery was undertaken because of hypertensive retinopathy, renal impairment and refractory hypertension. A thoracoabdominal to infrarenal aortic bypass was performed, using a 14-mm polyester (Dacron) graft (Meadox). The coeliac axis and upper two renal arteries on the left were implanted directly into the graft. At 7 months the blood pressure is easily controlled on reduced medication.

Patient 9. Right renal angioplasty and left renal autotransplantation to the iliac vessels was performed. The right renal artery occluded at 1 month resulting in nephrectomy. At 28 months the child is normotensive.

Patient 11. Left renal autotransplantation to the iliac vessels and right iliorenal saphenous vein bypass was performed. Death occurred on day 5 from multiple organ failure.

Discussion

MAS was first described more than 140 years ago[10,11], but many questions remain unanswered concerning the terminology, characteristics, aetiology, pathogenesis and treatment of the condition.

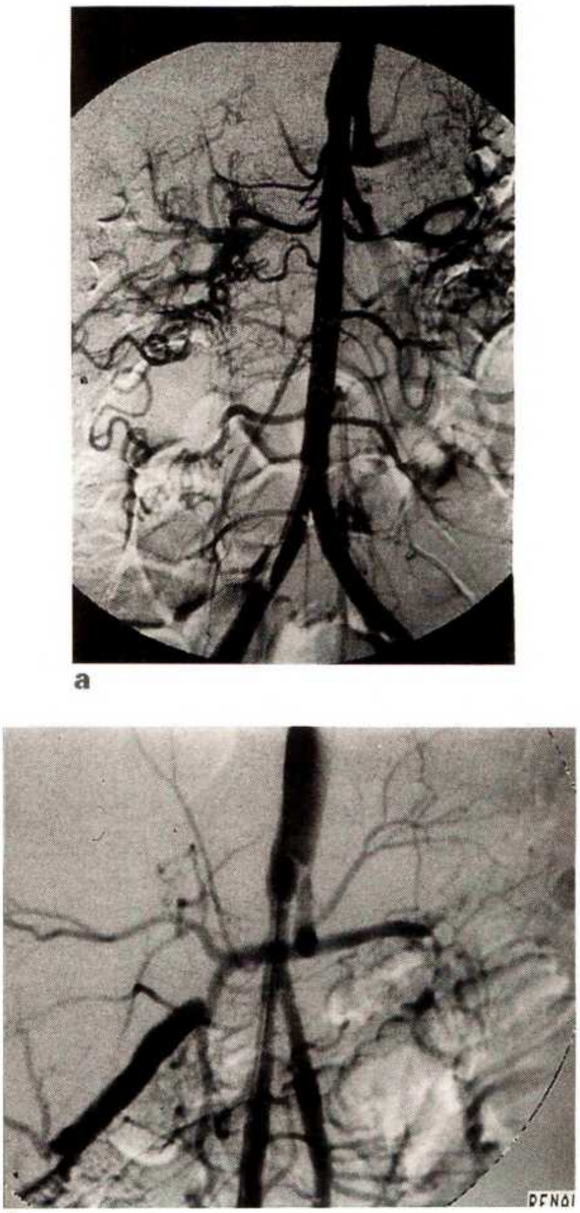

Fig. 3 Angiogram of patient 4 in 1994. **a** Stenotic origin of both left and right renal arteries with a widely patent coeliac axis. **b** Angiogram 3 months later. The vein graft (right gastroduodenal to renal artery) is aneurysmal while the left splenorenal bypass is almost occluded. Note that the coeliac axis is now compromised

Terminology

Segmental narrowing of the abdominal aorta is a rare but well recognized condition[5,7,12]. The majority of the reports refer to it as coarctation or hypoplasia[2,5–9,13–15]. The term coarctation is used exclusively for a congenital anomaly and multiple anatomical variants have been described[8]. Some authors use the term MAS to indicate an acquired (inflammatory) aetiology of the lesion, considering it as a variant of non-specific aortoarteritis (Takayasu's disease)[11,12], but this is controversial.

Furthermore, visceral aortic stenosis in association with neurofibromatosis is considered by some authorities as a different entity[1,2,16]. All these terms (coarctation, hypoplasia, neurofibromatosis and arteritis) relate to the aetiology of the lesion, which is unknown. MAS is the authors' preferred term as it describes a clinicoanatomical entity irrespective of its aetiology and pathogenesis.

Characteristics

The characteristics of MAS are summarized in *Table 3*. According to the literature[2,8,12–14] the mean age at presentation is 20 years. In this series the mean age at diagnosis was 7 years. We assume that severe stenoses present at an early age whereas less severe stenoses present later; the oldest reported patient was aged 50[15]. Another explanation could be the more intense health screening of children during recent years. The lesions may progress[1,3–5,12] and this was observed in one of the three children undergoing repeat angiography.

The associated findings are of interest. Four children in this series had neurofibromatosis despite the fact that hypertension is found in only 1 per cent of all patients with neurofibromatosis[17–19]. The relationship between neurofibromatosis and dysplasia of mesenchymal tissues, producing various vascular lesions (e.g. adventitial or intimal thickening or aneurysm formation) is well established[18], but its relationship to MAS suggests a more complex histogenesis. The association between MAS and Williams syndrome has been reported previously[1,20,21].

D'Abreu *et al.*[7] described multiple variants of abdominal aortic hypoplasia, while Robicsek and co-workers[5] and Hallett *et al.*[6] proposed a more functional classification (inter-renal suprarenal, infrarenal) to aid surgical decision making. However, review of the literature[1–4,8,9,14] indicates that the renal arteries are affected in 90 per cent of cases or more (100 per cent in this series). Other features include the presence of multiple renal arteries, the limited proximal extent of the lesion in most cases[1–4,8,14], with involvement of the coeliac axis and SMA in 50–70 per cent and sparing of the IMA.

Table 3 Characteristics of mid-aortic syndrome

Affects children or young adults
Causes hypertension rather than limb ischaemia
40% associated with neurofibromatosis
80% of patients have an epigastric bruit
Anatomical features
  Stenosis of the proximal abdominal aorta
  Renal artery stenosis in 90%
    Multiple renal arteries (90%)
    Ostial stenosis frequent (70%)
    Occasional mid-vessel stenosis
  Coeliac axis and SMA stenosed in 20–40%
  IMA almost never affected
  Huge collaterals (wandering artery of Drummond, intercostal, epigastric)

SMA, superior mesenteric artery; IMA, inferior mesenteric artery

Aetiology–pathogenesis

The exact aetiology of MAS is unknown. The young age of the patients suggests that it may be a congenital condition. The location of the disease at the origin of the aortic branches has been used to suggest that the process is primarily of aortic origin[12]. However, mid-vessel stenoses have been reported in the literature[19], especially in association with neurofibromatosis[16,19]. The commonly associated findings of neurofibromatosis, Williams syndrome or other congenital anomalies suggest a possible genetic component.

Histology of the aorta in three cases in this series showed only intimal and subintimal fibrosis with fragmentation of the elastic lamina but without any inflammatory changes, confirming previous reports[4,9,14]. These pathological findings are almost indistinguishable from those found in renal artery stenosis in children without MAS[16,19] and in some forms of fibromuscular dysplasia[22,23]. Several authors have suggested an inherited basis for fibromuscular dysplasia[23], while a familial incidence of renal lesions in neurofibromatosis has been reported previously[17].

The discrete focal distribution of MAS lesions has been attributed to the embryological development of the aorta and its branches. The prevailing theory first proposed by Arnot and Louw[24] suggests that MAS represents a failure of normal fusion of the two dorsal aortas. Other authors relate it to intrauterine injury or infection (e.g. rubella)[25]. The presence of multiple renal arteries, the extremely rare involvement of the IMA, and the fact that the aortic lesion is usually located between the coeliac axis and the IMA, suggest that MAS may be related to the embryological development of the kidneys. These develop at the pelvic brim and are first supplied by a prolongation of the dorsal aorta (the median sacral artery) which subsequently becomes obliterated. As the kidney migrates up the posterior abdominal wall, it is successively supplied by a series of branches from the abdominal aorta, which originate between the coeliac axis and the IMA. Most of them are obliterated by an unknown process similar to that of ductus arteriosus obliteration. An extension of this process to the aorta might cause MAS.

Treatment

The natural history of untreated symptomatic MAS is invariably death before the fourth decade[14]. Björk and Intonti[26] reported a series of 14 patients in which the average age of death was 30 years. In the series of Deal *et al.*[19], two of 11 children died before reaching adolescence. MAS in childhood is difficult to manage because of uncontrollable hypertension and deterioration in renal function[1,14,16], which are the main indications for surgery[1,12,13,27]. The timing of surgical intervention is controversial and difficult to decide, although easier in adolescents and young adults in whom surgery is more acceptable. A thoracoabdominal to infrarenal aortic bypass, with reimplantation of the renal arteries directly into the graft[8,12–14], is the procedure of choice in this older age group. However, a single-stage definitive repair at a young age requires a change of graft as the patient grows. Procedures such as splenorenal or hepatorenal bypass[28,29] can be performed if the coeliac axis is not compromised. Renal autotransplantation with *ex vivo* arterial reconstruction[30,31] is safe, but may result in continuous hypoperfusion of the kidneys if the aortic stenosis causes a substantial pressure drop in the infrarenal aorta. If there is good inflow, autotransplantation is a valuable method, providing prosthetic grafts are not used[32]. A thoracoabdominal to infrarenal aortic bypass, together with bilateral renal autotransplantation to the iliac vessels or direct implantation of the renal arteries into the graft, is another option. Children have a broad subcostal angle which allows exposure of the aorta with abdominal medial visceral rotation avoiding division of the diaphragm or thoracotomy[33]. Veins can also be used as conduits but dilatation of the vein graft can occur quickly[34]. All these factors contribute to the high reoperation rate in children with MAS[12–14,19,27].

PTA of the renal lesions might, theoretically, be helpful but its role is not yet clear. The success rate of PTA in children with renal artery stenosis varies, but is usually around 30–50 per cent[3,4,16,19]. The extensive nature of aortic and renal lesions in MAS generally forms a contraindication to PTA. Two patients underwent attempts on three occasions in this series with poor result, confirming the experience of others[3,4,19]. Fry[27] states that there is little point in dilating the aortic narrowing, but some selected aortic stenoses may respond to repeated angioplasty using larger balloon diameters on each occasion[19,32].

The authors suggest that children younger than 6 years old should be treated medically and emphasize that every effort should be made to avoid surgical intervention, even if renal function deteriorates. If surgery must be undertaken, a splenorenal or hepatorenal bypass may be performed if the coeliac axis is not stenosed. Otherwise, thoracoabdominal to infrarenal aortic bypass with renal artery reconstruction and/or autotransplantation is the procedure of choice. This may require further surgery to treat the disparity between the graft and native vessels as the child grows and so comprehensive follow-up is essential. Any deterioration in renal function following surgery should be investigated with angiography and any stenosing lesion should be corrected without delay.

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Amputation rates as a measure of vascular surgical results

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Reconstructive surgery for critical leg ischaemia (CLI) increased in both hospital- and population-based patient samples over 12 years. In the referral centre amputation numbers were unchanged over this period, although amputation carried out for patients with CLI decreased from 58 to 35 per cent. In the population sample amputation numbers decreased by 25 per cent and amputations of patients with CLI decreased from 79 to 43 per cent. Patient characteristics and amputation patterns were different in the two settings. Amputation rates as a measure of the efficacy of an arterial reconstruction policy should be used only on a population basis. The analysis is skewed by selection bias in referral centres.

The results of reconstructive arterial surgery for critical leg ischaemia (CLI) are generally evaluated by the duration of patency of the reconstruction and limb salvage rate. Many clinical series describe high rates of limb salvage[1,2], but they may not be representative as some reports from different settings describe conflicting results[3–8]. The present study was undertaken to compare reconstructive arterial surgery and amputations in two different clinical settings with the aim of identifying a relevant basis for reporting limb salvage and amputation rates.

Patients and methods

A retrospective study was undertaken of amputations and arterial reconstructions for CLI in a vascular referral centre (Helsinki University Hospital (surgical hospital)) and a population setting (Vasa Central Hospital). The former hospital serves as one of two referral centres for vascular surgery in southern Finland around Helsinki (total population 1 260 000) and performed half of the vascular procedures in the area as registered in the National Vascular Registry, *Finnvasc*, in 1991–1992. As the hospital performs all kidney transplantations in Finland it has a high proportion of patients with renal insufficiency. In the same region 15 other hospitals perform amputation and some also carry out arterial reconstruction. Vasa region (including one central and two district hospitals) has a defined population catchment area (165 000 inhabitants), with almost total coverage of all vascular surgery and amputation in the area. Vascular surgery is performed in the Vasa Central Hospital, while the district hospitals perform amputation and, occasionally, thrombectomy. The policy for reconstructive arterial surgery in the leg is uniform in both hospitals, with preference given to reconstructive treatment of CLI since 1980.

For this study amputations were defined as follows: those performed primarily for acute ischaemia or in close association (30 days) to its vascular or endovascular treatment were considered acute ischaemia amputations; amputations performed within 30 days of an elective procedure were considered postreconstructive amputations; and all other amputations were defined as primary.

According to hospital discharge and operation records, 487 amputations were performed in the surgical hospital and 498 in the Vasa region from 1st January 1980 to 31 December 1991. Patient characteristics and detailed information concerning amputation were available in 99·5 per cent of patients in the surgical hospital and 92·0 per cent of patients in the Vasa region. Data on age, sex, primary amputation level and survival were obtained for all patients.

Differences in patient characteristics, level of amputation and relationship of amputation to acute and elective arterial reconstruction were analysed for both settings. Change in amputation patterns was analysed for three consecutive 4-year intervals. Comparison of the patient groups was made using the χ^2 test.

Results

Over time the number of patients treated for CLI increased in the referral centre from 52 to 99 per annum, and in the population setting from 56 to 75 per annum. Reconstructions for leg ischaemia generally and especially for CLI increased in both settings. In the referral centre reconstructions for CLI increased by a factor of 2·5 and in the population setting by 3·3 (*Fig. 1*). The numbers of amputations each year did not change (about 40) in the referral centre, while the patients' mean age decreased from 71 to 66 years. In the population setting amputations decreased from 48 to 36 per annum, with an unchanged patient mean age of 77 years. The overall amputation rate for patients treated for CLI decreased in the referral centre from 58 to 35 per cent and in the population setting from 79 to 43 per cent. Postoperative amputation rates after reconstruction for CLI decreased in the referral centre from 20 to 13 per cent and in the population setting from 14 to 6 per cent. The rate of amputation for acute ischaemia remained unchanged during the period of study.

In the referral centre more amputations were performed after reconstruction; there was a higher proportion of primary amputations in the population setting (*Table 1*). Patients having primary amputation in the population setting were older, with more women and a higher incidence of cerebrovascular risk factors. In the referral centre more patients had had previous vascular surgery and renal insufficiency was commoner (*Fig. 2*), increasing from 8 per cent in the early study period to 17 per cent in the late period. Patients with renal insufficiency were younger, with a mean age of 62 years, than other patients. Below-knee amputations were performed more frequently in the referral centre. The postoperative mortality rate was higher in the population setting (*Table 1*).

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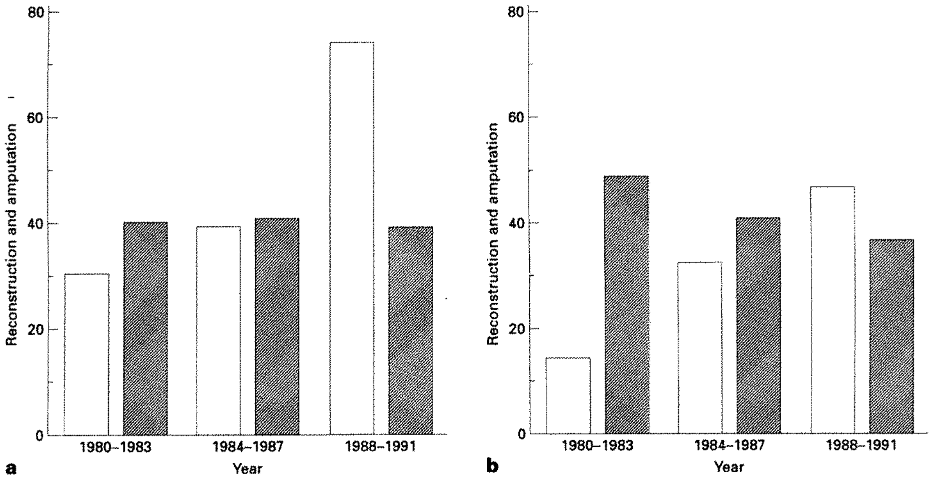

Fig. 1 Change in annual number of reconstructions for critical leg ischaemia (□) and amputation (▨) **a** in the surgical hospital and **b** in the Vasa region

Table 1 Type of amputation and characteristics: surgical hospital and Vasa region 1980–1991

Type of amputation/characteristics	Surgical hospital	Vasa region	*P*
Primary			
No. of procedures	338 (69·4)	426 (85·5)	$0{\cdot}005 > P > 0{\cdot}001$
Mean age (years)	69	77	
Men (%)	50	38	$0{\cdot}005 > P > 0{\cdot}001$
Diabetes (%)	51	50	n.s.
Below-knee amputation (%)	63	20	$0{\cdot}005 > P > 0{\cdot}001$
Postoperative mortality (%)	7	23	$0{\cdot}005 > P > 0{\cdot}001$
Postreconstruction			
No. of procedures	93 (19·1)	27 (5·4)	$0{\cdot}005 > P > 0{\cdot}001$
Mean age (years)	69	75	
Men (%)	71	41	$0{\cdot}01 > P > 0{\cdot}005$
Diabetes (%)	36	63	$0{\cdot}05 > P > 0{\cdot}025$
Below-knee amputation (%)	41	44	n.s.
Postoperative mortality (%)	11	20	n.s.
Acute ischaemia			
No. of procedures	56 (11·5)	45 (9·0)	n.s.
Mean age (years)	76	76	
Men (%)	46	38	n.s.
Diabetes (%)	21	38	n.s.
Below-knee amputation (%)	16	18	n.s.
Postoperative mortality (%)	25	38	n.s.

Values in parentheses are percentages. n.s., Not significant; χ^2 test

Discussion

Evaluation of the outcome of arterial reconstructive surgery in the legs by limb salvage and amputation rates is hampered by many confounding factors. The change over time in amputation rate reflects changes in both treatment policy and patient population. In the study by Pohjolainen and Alaranta[9], it was predicted that major amputations should increase as the proportion of older age groups increases. Selection of patients by referral, reconstruction method or exclusion criteria skews results. Changes in the population and inadequate follow-up result in a loss of patients and reduce the reliability of conclusions. Few published series describe a defined population with total vascular surgical cover over an extended period[10–13].

This study compares arterial reconstruction and amputation data within a vascular referral centre and defined population setting. The arterial reconstruction policy for CLI was similar in both settings, and during the period of study increasing numbers of patients were treated in each. The proportion undergoing reconstruction increased, with a decrease in the proportion undergoing amputation. The total number of amputations in the referral centre was unchanged, however, probably reflecting an increase in patients with CLI unfit for reconstruction and so requiring amputation. Patients were selected at primary or secondary treatment levels before admission to the referral centre. In the population setting all patients with CLI or acute ischaemia were covered by the study for the whole period. In this setting an association between increasing numbers of reconstruction and decreasing amputation rates is seen, probably reflecting a true impact of reconstructive arterial surgery on the outcome of CLI[10,11,13]. The age structure, patient characteristics, high rate of primary amputation and high postoperative mortality rate in the population setting probably represent an accurate picture of the disease

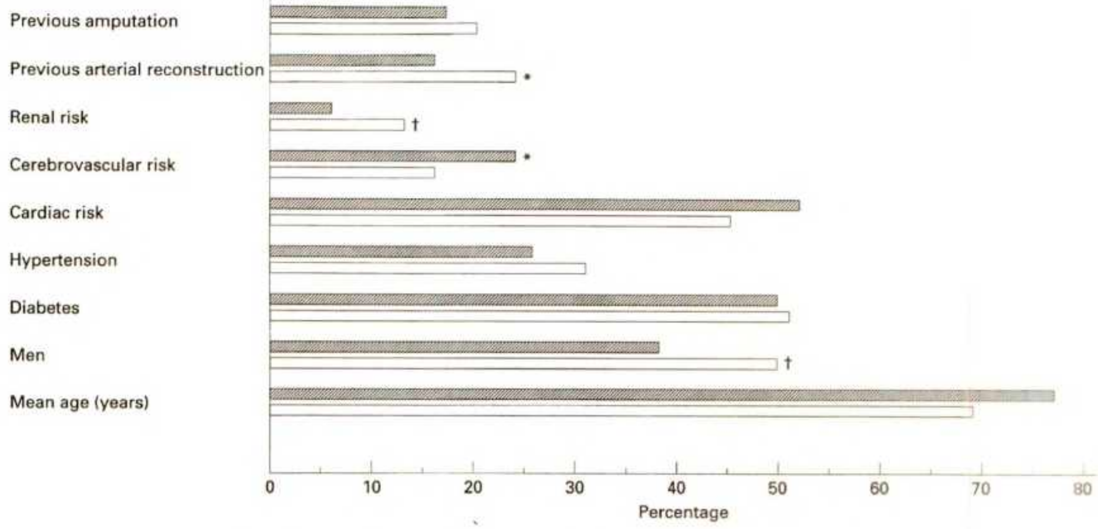

Fig. 2 Characteristics of patients who underwent primary amputation in the surgical hospital (□) and Vasa region (▨) between 1980 and 1991. $^{*}P<0{\cdot}025$, $^{\dagger}P<0{\cdot}005$, χ^2 test

without prehospital or inhospital selection[10]. The patient characteristics in this setting differed considerably from those of patients having primary amputation in the referral centre, where the patients were younger and had had more previous vascular surgery. There was a subset of patients with renal insufficiency and a lower percentage of endangered legs being amputated in the referral centre throughout the study period. This indicates referral selection before treatment. A substantial number of older patients with CLI undergo amputation in hospitals without vascular surgical consultation[14]. Only recently has the positive effect of an aggressive reconstruction policy been shown also to apply in the older age group, suggesting that all patients with a potential for independent or semi-independent living should be considered for reconstruction, irrespective of age[2,10,11,13].

A high proportion of below-knee as opposed to above-knee amputation is viewed as a main goal in achieving mobilization after amputation[15–18]. The advanced age of the unselected patients in the population setting, associated with an apparent high proportion of bedridden institutionalized patients, explains the low below-knee to above-knee amputation ratio. It underlines the problem of comparing amputation rates and levels in different settings without clear reference to patient characteristics.

Acknowledgements

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Surgical workshop

Intra-arterial lignocaine in embolectomy

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Acute limb ischaemia is now commonly treated by thrombolysis, but embolectomy remains a good and appropriate operation in certain cases of embolism. The patient with an acutely bloodless limb, sensory loss and an obvious source for embolus (such as atrial fibrillation) may be best treated by this means. Embolectomy is usually done under local anaesthesia, infiltrating the groin or antecubital fossa to expose the femoral or brachial artery. The one part of the operation that often causes pain is withdrawal of the inflated embolectomy balloon along the arteries to remove thrombus and clot. Although it is common practice to warn patients that they may feel discomfort during this manoeuvre, it can still prove quite distressing to some patients.

Guided by the work of van Niekerk and Coetzee[1] on regional analgesia, the authors have used 0·5 per cent lignocaine during arterial embolectomy to relieve the pain of balloon withdrawal.

Surgical technique

Four patients (two men) underwent brachial embolectomy under local anaesthesia. During the first withdrawal of the embolectomy catheter, two patients (aged 87 and 88 years) experienced obvious discomfort, while two (aged 44 and 63 years) when questioned reported that they had felt pain. In each case 8–10 ml 0·5 per cent lignocaine was then infused into the arteries through a number 6 umbilical catheter, with its tip placed 2–3 cm into the vessel from the arteriotomy. After a 2-min interval further catheter passages were done, with no signs of pain in either elderly patient, and reports from the two younger patients that the discomfort had been virtually eliminated. Electrocardiographic monitoring showed no changes suggestive of any cardiac effect of lignocaine during the operation.

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Discussion

It is a basic principle of surgical management to relieve any needless pain. Withdrawal of balloon embolectomy catheters is well recognized as a potentially painful element of embolectomy, but intra-arterial local anaesthesia has not been promoted as a method of analgesia during this procedure.

The use of intravenous lignocaine is well recognized in orthopaedic surgery, but intra-arterial administration is less familiar. It was used to relieve pain and spasm by Leriche in 1935[2], and its use for this purpose was also documented by Auger[3] and Hankiss[4]. It has been described as a method of providing regional analgesia (when administered with a tourniquet on the limb) by van Niekerk[1], who used 5–50 ml in the upper limb. This experience, together with an estimate of the volume required to fill the main arteries and knowledge of toxicity thresholds, guided the choice of a 10-ml bolus as likely to be both effective and safe. This proved to be the case in practice. The authors continue to use this method and recommend it as an adjunct to pain relief during embolectomy.

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Magnetic resonance imaging in the management of diabetic foot infection

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A prospective study was carried out of 22 patients admitted with 25 diabetic foot infections. All had cellulitis, 12 had discharging ulcers and eight had digital gangrene. In one case magnetic resonance imaging (MRI) was unhelpful owing to patient movement. Thirteen scans suggested deep-seated infection, including abscess (ten), osteomyelitis (seven) and ankle effusion (one). Overall, imaging provided a specificity of 77 per cent, a positive predictive value of 77 per cent, a sensitivity of 91 per cent and a negative predictive value of 91 per cent. MRI is valuable in determining the presence and extent of infection, which allows appropriate planning of surgical intervention.

Damage to the foot in diabetes mellitus is due to a complex interplay between infection, neuropathy and peripheral arterial disease[1]. Infection may be superficial or deep, with extensive tissue necrosis. The diabetic foot accounts for more days in hospital than all other complications of diabetes[2], and patients with diabetes are 15 times more likely to have a major amputation than the rest of the population[3]. Only half of diabetics undergoing lower-limb amputation survive beyond 3 years[3,4].

Prevention of the problem is clearly the ideal[5]. Once diagnosed, the principle of management is to drain collections of pus and remove all necrotic tissue. The peripheral vasculature requires assessment. Patients with diabetes often have occlusive disease of calf arteries, with relative sparing of the more proximal arteries. Calf vessel occlusion may be amenable to distal reconstruction[6,7]. No patient with diabetes should have an amputation without prior angiography unless the limb is not salvageable at the time of presentation[8]. Exploration of a foot which does not have a deep-seated infection may cause irreparable damage, and so the need for debridement or amputation must be carefully balanced against the possibility of tissue conservation. Accurate assessment of the extent of infection clearly aids in deciding which course to take. Magnetic resonance imaging (MRI) has been shown to be useful in identifying musculoskeletal pathology[9,10]. The aim of this study was to evaluate the role of MRI in planning surgical intervention in the infected diabetic foot.

Patients and methods

Twenty-two patients (14 men and eight women) with diabetic foot infection sufficiently severe to require hospital admission were studied prospectively. Ten patients were insulin-dependent diabetics. The median age was 67 (range 23–86) years. All patients had cellulitis; in addition 12 had discharging ulcers and eight digital gangrene. The median length of history before admission was 4 (range 1–16) weeks. Five patients were pyrexial and the median white cell count (WCC) was 10·9 (range 5·0–19·8) × 10^9/l. Four patients had previously undergone one or more operations on the affected foot. These operations comprised four toe amputations, two mid-metatarsal amputations and one debridement. In addition four patients had had operations to the other leg, including three debridements and two below-knee amputations.

All patients were initially treated with intravenous metronidazole, flucloxacillin and benzyl penicillin. Bed rest and local foot care were started. Peripheral pulses were examined and ankle:brachial arterial pressure indices calculated. Arteriography was carried out if indicated. All patients had plain radiography of the affected foot and MRI. Management was not based on the results of MRI.

Earlier scans were carried out on a General Electric Max 0·5T unit (IGE Medical Systems, Slough, UK); later scans were performed with a GE Vectra II 0·5T machine (IGE Medical Systems). All patients were scanned by means of a head coil with the foot held in neutral position. Initially T_1-weighted (TR400, TE25) T_2-weighted (TR780, TE25) sagittal and axial scans, and short tau inversion recovery (STIR) (TR2000, T_1 100) sagittal scans were carried out. T_2-weighted scan sequences are no longer used; only T_1-weighted and STIR sequence sagittal and axial scans are currently employed. Slices of 5 mm were examined, with a 1-mm gap between scans. The procedure takes 20–30 min to complete.

Outcome was determined on the basis of operative findings or clinical condition of patients continuing with conservative treatment.

Results

The 22 patients required 25 hospital admissions and thus 25 MRI scans were performed during the period of the study. The median follow-up from time of admission was 9 (range 1–18) months. Operative treatment was carried out shortly after admission on 12 occasions (*Fig. 1*). Several patients required more than one operation. The procedures performed were debridement alone (six

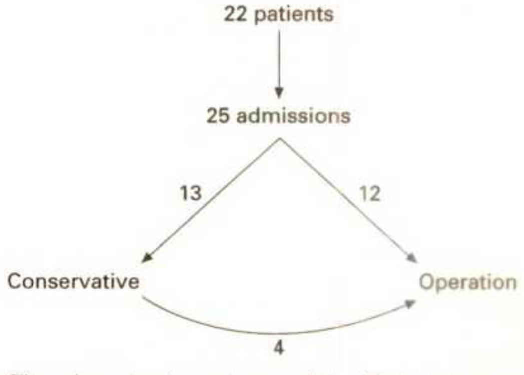

Fig. 1 Flow chart showing outcome of the 25 admissions to hospital

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Table 1 Comparison of magnetic resonance imaging findings with clinical outcome

	Clinical findings		
MRI findings*	Infection present	Infection absent	Total
Infection			
Present	10	3	13
Absent	1	10	11
Total	11	13	24

*Magnetic resonance imaging (MRI) unsatisfactory due to patient movement in one case

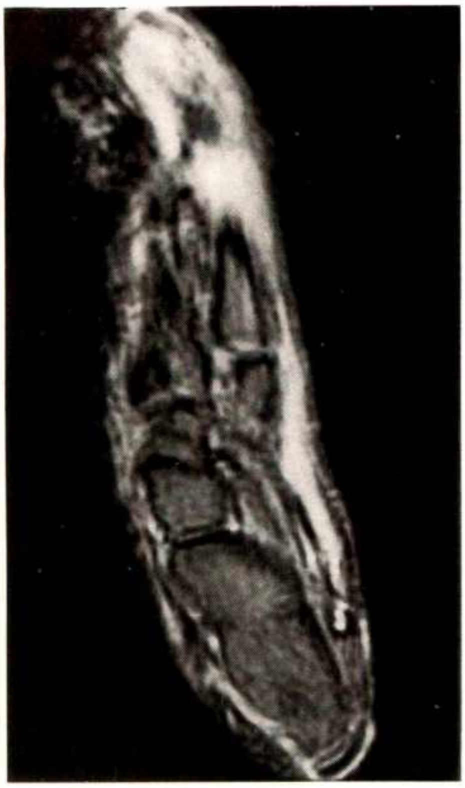

Fig. 2 T_2-weighted image of a right foot, showing extensive high-signal change in the soft tissues on the medial side of the foot, particularly around the big toe in plantar soft tissues. High-signal change is also seen in the first metatarsal and phalanges. Osteomyelitis with inflammatory change in the soft tissues was confirmed at operation

patients), debridement with amputation of toe(s) (eight), toe amputation alone (one), mid-metatarsal amputation (one) and below-knee amputation (three). One 86-year-old woman died from pulmonary embolism 3 weeks after major amputation. On 13 occasions conservative treatment was continued. Four patients ultimately required a surgical procedure; in three this was simply to amputate a mummified toe, while one patient required amputation of the hallux due to soft tissue necrosis and osteomyelitis. Angiography was carried out on 15 patients. Percutaneous transluminal angioplasty was undertaken in seven patients and distal reconstruction in two.

Neither WCC nor presence of pyrexia was helpful in predicting deep-seated infection. Plain radiography of the foot showed osteomyelitis in two patients, septic arthritis in one and soft tissue infection in two. One of the MRI scans was unhelpful because the patient was unable to remain still throughout the investigation. The results in the remaining 24 patients are shown in *Table 1*. Thirteen scans suggested one or more deep-seated foci of infection within the foot (osteomyelitis, seven; abscess formation, ten; ankle effusion, one) (*Figs 2* and *3*). In one patient with cellulitis the initial MRI scan showed no evidence of infection. She failed to settle with conservative treatment and the scan was repeated 1 month later. On this occasion calcaneal osteomyelitis was demonstrated. In nine cases MRI findings were confirmed at operation and by histological and microbiological examination of excised tissue. One patient, with an area of suppuration on the hallux, settled conservatively after pus drained spontaneously. The remaining three patients were treated conservatively: two improved and the scan results were not confirmed at operation in one. The scan showed no evidence of deep-seated infection in 11 patients and in only one was infection later demonstrated. MRI provided a specificity of 77 per cent and a positive predictive value of 77 per cent. Sensitivity was 91 per cent with a negative predictive value of 91 per cent.

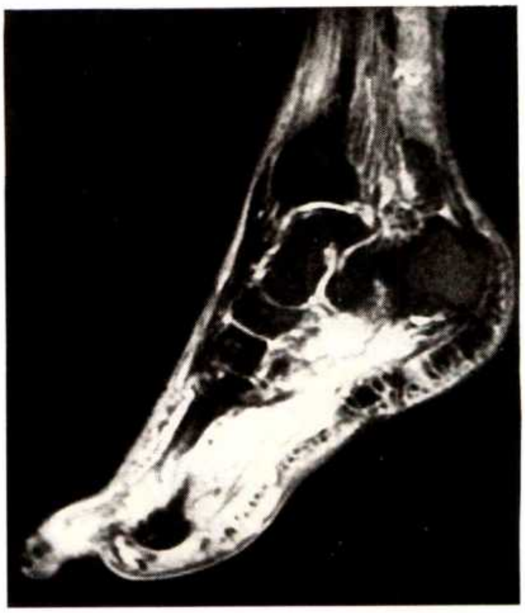

Fig. 3 Sagittal short tau inversion recovery image of a left foot, showing a soft tissue abscess on the plantar surface with high-signal change in the metatarsal heads of the first and second toes. Osteomyelitis and abscess were confirmed at operation

Discussion

It has been shown that the major amputation rates associated with ischaemic and neuropathic diabetic foot ulcers can be reduced by a combined treatment approach in a specialized clinic[11]. This involves close cooperation between chiropodists, shoe fitters, nurses, physicians, and vascular and orthopaedic surgeons. Inevitably some patients present with such severe tissue loss that major amputation is the only measure that will save life.

Clinical features, such as pyrexia and increased WCC, have little role to play in predicting whether surgical exploration is necessary. In this series both were unhelpful. Plain radiography is poor at detecting foot infection because end-stage tissue destruction needs to be present before identification can be made[12]; up to 50 per cent of bone must be lost before it becomes radiologically apparent[13] and this may take 10–14 days. Clearly this does not aid in early detection and in the present study plain radiography was not helpful.

Radionuclide scanning with technetium-99 methyl diphosphonate or gallium-67 citrate is useful for identifying inflammatory and infective changes. Although sensitivity is high, specificity is low. Arthritis, acute fracture or recent operation can all produce false-positive results[12,14]. It often takes 24–48 h to complete the scan and anatomical detail is poor, making subsequent surgical planning difficult.

More recently leucocytes labelled with indium-111 have been used[15,16]. This method is associated with increased specificity but it is time consuming to prepare and expensive[14]. A small clinical study has suggested that it is more sensitive than MRI in detecting osteomyelitis[17]; overall the accuracy of the two techniques was similar. Computed tomography (CT) is able to localize infection but does not define accurately its proximal extent[18]. MRI has been shown to be effective in defining the surgically important conditions of cellulitis, abscess formation, infected tenosynovitis and osteomyelitis in the diabetic foot. In addition it can identify oedema and neuro-arthropathy[19]. MRI has several advantages over the other methods of imaging that have been discussed. There are fewer false-positive scans compared with scintigraphy[20]. In rabbit models, where the long bones are of a similar size to bones in the human foot, MRI is better than scintigraphy at identifying soft tissue infection[21]. No difference was found between these techniques in their ability to demonstrate bony infection. MRI is also better at defining soft tissue than CT[10]. Obtaining multiplanar images is of great benefit when planning operation. MRI, therefore, provides an accurate, non-invasive method of assessment. Studies may be performed rapidly and, in the present series, all examinations were completed within 30 min. Other workers[22–24] have also found MRI to be accurate in identifying diabetic foot infection.

MRI provides useful information in terms of both positive and negative predictive value. A negative scan gives the clinician confidence to persevere with a conservative policy. Clearly, should the patient not improve, it is worth repeating the scan as illustrated by one of the present patients in whom the initial scan was negative but a repeat scan 1 month later showed the development of osteomyelitis. If a patient fails to settle satisfactorily, despite having sepsis or necrosis dealt with surgically, MRI should be considered. It has been shown[22] to be reliable in identifying pockets of infection not found at operation.

MRI is useful in identifying early infective complications of diabetic feet. It should allow accurate planning of surgical intervention, resulting in less extensive tissue damage. In addition to identifying osteomyelitis, this study has demonstrated that MRI accurately reveals deep-seated soft tissue infections in the absence of bony infection. Intervention before the development of osteomyelitis allows greater tissue conservation.

Early MRI also permits a more confident approach to conservative treatment in patients with negative scans, which is vital when the consequences of lower-limb amputation are considered. It is important that MRI be used in conjunction with clinical findings. It is an accurate and rapid method of assessment that can easily be repeated in patients failing to settle with conservative measures. Its role in the management of diabetic foot infection merits wider use.

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For debate

Relation between aetiology and treatment of leg ulcers

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The author's leg ulcer unit has been involved in compression methods for 45 years[1]. During this time views expressed by its clinicians on compression and its relevance to the aetiology of ulceration have developed in parallel. This differs from the situation in other centres, where the cause of such lesions has so far been examined in detail only in the ulcerated leg itself. The situation found in such limbs includes 'venostasis', leg oedema, arteriovenous shunts, free radicals, pericapillary fibrin cuffs, micro-oedema, and vessel plugging by leucocytes and microthrombi. By contrast the author's unit has approached the problem from the perspective of the normal limb. The physiological vulnerability of any limb has been used as a model for the vulnerability of the varicose limb. A compression treatment regimen counteracts two simple gross determinants of ulceration; first, the pressure amplitude changes during exercise and, second, the pressure gradient. This broad conceptual approach has allowed the identification of important relationships which have long since been buried beneath the wealth of what the author believes to be a secondary phenomenon recorded in the literature.

Vulnerability of the normal leg

Various exogenous factors can render the normal leg vulnerable, e.g. trauma, rheumatoid arthritis, diabetes, tuberculosis, sickle-cell anaemia, psoriasis and lichen verrucosus. Some of these diseases may actually present as non-venous ulcers. More importantly, however, just as venous ulcers are associated with ambulatory venous hypertension, so too in normal legs there exists a similar physiological hydrostatic venous hypertension. Thus, in the vertical position the perfusion pressure in the legs, both on the arterial and venous side of the circulation, is raised. When walking, the calf pump action can reduce this hydrostatic effect. The resulting arteriovenous pressure gradient is actually greater than during recumbency. Stretching of the vascular smooth muscle (because of the rise in blood pressure) also affects tissue perfusion[2,3]. This mechanism helps maintain the stability of the whole circulation during postural changes.

This vasoconstriction in vertical healthy individuals is compensated, particularly on exercise, by an increased perfusion pressure. If the compensation is only partial, however, the normal leg becomes vulnerable.

Venous insufficiency

Persistent venous hypertension in venous insufficiency becomes a strong vasoconstrictive stimulus which almost certainly impairs tissue nutrition. For most of the time the maximum venous blood column equals the hydrostatic increase on the arterial side. In other words, gravity acts equally on the outflow and inflow of the limb circuit.

Venous ambulatory hypertension, therefore, causes harm in two ways: (1) the advantage of the arteriovenous perfusion pressure drop is lost when compared with that of the normal leg, and (2) chronic venous hypertension may produce vasoconstriction due to the venoarterial reflex, a fact reported by Dodd *et al.*[4] who emphasized the changes of tissue perfusion with posture. The author has also put forward similar arguments at an earlier date[5] on the basis of clinical observations.

Simplified hydrostatic compression

The cornerstone of the treatment of leg ulcers is compression[1]. Clearly, if the aforementioned principles are important any successful compressive mechanism should seek to reverse the vicious cycle. One such method has been described by the author's clinic[6]. It is a simplified hydrostatic compression combining the two compression principles. The first of these was described by Wood[7]. Compression is achieved by a water cushion under an Unna boot connected to a water reservoir at heart level. The hydrostatic pressure so generated corresponds closely to the limb's venous pressure in any body position and at all levels. The second principle (mitigating the poor calf pump) translates into an inflatable boot[8]; body-weight is used to counteract and support the deficient calf pump.

Experience has taught clinicians that the latter alone is sufficient in most instances to promote healing, i.e. the complete pressure gradient is replaced by a modified gradient. The tread-out principle is simply initiated by prolongation of the distal end of the cushion as far as the sole. The leg muscle pump is thus strengthened by the tread-out water volume at each step. The tension in the bandage self adjusts with posture; this type of bandage overcomes many problems experienced with conventional bandaging techniques[9,10].

Apart from Linser's 'inflated boot'[11], both Scott's[8] and Wood's[7] primary reports are rarely quoted. Wood's idea failed to be revived despite Chant's clear isotopic demonstration of the effects of using hydrostatic compression[12,13]. Following success in the author's clinic these methods have been accepted by several Czech and Slovak health centres; the results have been reported in local journals.

Theories of the aetiology of ulcers usually show a striking disregard of these important facts. Scott's[8] and Wood's[7] ideas have remained forgotten worldwide, as have approximately 15 pertinent reports from the author's department. In contrast, the literature is full of advanced techniques that demonstrate blood flow changes under leg compression, etc. Temple and Burkitt[14] note that dissection of a whole organism into its components proves easier than their reintegration, which is always restricted by tunnel vision. The Nobel Laureate Lederberg[15] warns against reductionism with consequent loss of perspective to both the whole organism and clinical practice. In phlebology the fact that support (particularly the kind described here) heals ulcers has been neglected.

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Invited comment

Dr Holan's argument seems to run thus. All lower limbs, whether diseased or not, are subjected to similar raised hydrostatic pressures in the vertical position. However, in non-diseased limbs normal protective mechanisms, such as the so-called venoarteriolar reflex, counter the added pressures. He also quotes my own and others' work which shows that an external counter pressure equal to the intravascular hydrostatic pressure minimizes these 'reflex' changes and promotes better ulcer healing. Dr Holan, therefore, concludes that the breakdown of the perfusion regulation mechanism is the cause of ulceration.

Parts of this argument, I believe, are incorrect, although I *almost* agree with the conclusion. My counter argument goes as follows. Yes, certainly all lower limbs in the upright position are subjected to increased pressures. However, the voltage clamp experiments of Lansman *et al.*[1] suggest that it may be a local mechanical regulation of the smooth muscle which gives protection. It would seem that the differential between the intracapillary pressure (Pc) *and* tissue pressure (Pt) is crucial. As well as regulating capillary flow this regulatory effect almost certainly controls transcapillary fluid movement. Indeed, my results[2], kindly quoted by Dr Holan, fit the Starling law equation practically perfectly[3]. It seems, therefore, that the hydrostatic stocking by keeping the differential pressure (Pc – Pt) constant maximizes what capillary flow there is and therefore aids healing.

On the subject of the aetiology of the ulcers *per se*, I have previously hypothesized[2], demonstrated by computer modelling[4], and more recently using tensiometers and laser Doppler techniques[5–7], that the mechanics and biological properties of the skin of controls and patients with venous disease differ significantly. Stresses and strains in and around the gaiter are, theoretically, reversed by the hydrostatic support described. In brief, I think the authors are right for the wrong reasons, i.e. the hydrostatic counter pressure reverses the stresses and strains experienced in the gaiter area, thereby allowing the perfusion regulatory mechanisms to return to normal and so enabling repair work to begin.

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Role of neutrophil–endothelial adhesion in skeletal muscle reperfusion injury

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During postischaemic revascularization neutrophil–endothelial adhesion in the skeletal muscle microcirculation, promoted by the neutrophil adhesion molecule Mac-1, may impair muscle blood flow and release oxygen free radicals and proteolytic enzymes which causes further tissue injury. This study has assessed the effect of an anti-Mac-1 monoclonal antibody on the severity of skeletal muscle injury in a rat model of 6-h hindlimb ischaemia and 4-h reperfusion. In control animals a sustained impairment of muscle perfusion was associated with neutrophil sequestration, muscle infarction and muscle oedema ($P < 0.001$ *versus* normal rats). In contrast, intravenous administration of anti-Mac-1 monoclonal antibody before revascularization prevented neutrophil recruitment, reduced muscle necrosis and improved postischaemic muscle perfusion at 120 and 240 min (not significantly different from normal), thus confirming that neutrophils are important cellular mediators of skeletal muscle reperfusion injury. Monoclonal antibodies targeting neutrophil adhesion molecules may, therefore, have a role in the prevention of this complication of limb revascularization.

Revascularization of ischaemic skeletal muscle is essential for successful limb salvage but, paradoxically, may initiate biochemical and cellular events which exacerbate the hypoxic tissue injury[1–3]. Initially, oxygen free radical generation promotes the release of neutrophil chemotactic agents[2] which is followed by the liberation of powerful cytotoxic oxidants and toxic proteolytic enzymes from activated neutrophils[4].

The occurrence of both systemic neutrophil activation after ischaemia and reperfusion, and the accumulation of neutrophils within reperfused muscle and remote organs suggests that neutrophils have an important role in the pathogenesis of skeletal muscle reperfusion injury[5–7]. Furthermore, animal studies have shown that neutrophil depletion reduces postischaemic muscle injury[8,9]. A prerequisite for neutrophil-mediated tissue injury is neutrophil adhesion to the microvascular endothelium[10]. This interaction is dependent on a receptor–ligand mechanism between corresponding receptors on the surface of neutrophils and the endothelium. Chemotactically activated neutrophils adhere to the endothelium through their cell surface molecule Mac-1 (CD11b)[10,11]. This study investigated the effect of an anti-Mac-1 monoclonal antibody on the severity of skeletal muscle injury in a rat model of hindlimb ischaemia and reperfusion.

Materials and methods

Animal preparation

The rodent model of hindlimb ischaemia and reperfusion used has been described previously[12]. Briefly, male Sprague–Dawley rats weighing 300–400 g were anaesthetized with pentobarbitone (60 mg/kg intraperitoneally) and mechanically ventilated through a tracheostomy. A cannula was inserted into the external jugular vein for intravenous fluid or drug infusion. Unilateral hindlimb ischaemia was produced by applying an elastic band tourniquet proximally on the thigh. Gastrocnemius muscle neutrophil content, viability, oedema and perfusion were assessed in four separate experiments.

Experimental groups

Three groups of animals were studied: normal rats (10-h general anaesthesia, no ischaemic insult to either hindlimb); control rats (6-h unilateral hindlimb ischaemia and 4-h reperfusion), and rats receiving anti-Mac-1 monoclonal antibody (6-h unilateral hindlimb ischaemia and 4 h reperfusion).

Monoclonal antibody

A mouse immunoglobulin (Ig) G_{2a} (IgG_{2a}) (MRC OX-42; Serotec, Oxford, UK)[13] to the Mac-1 (CD11b) receptor was administered intravenously (total dose 230 μg) in a volume of 1 ml phosphate buffered saline (pH 7·4) 30 min before reperfusion. Flow cytometric analysis confirmed specific binding of the antibody to rat neutrophils. Control and normal rats received 1 ml saline without antibody

Myeloperoxidase assay

Muscle neutrophil content was assessed by measurements of the neutrophil-specific enzyme myeloperoxidase in gastrocnemius muscle harvested from the study limbs of normal rats ($n = 10$), controls ($n = 10$) and anti-Mac-1-treated animals ($n = 10$) Myeloperoxidase was determined by a modification of published methods[6,14]. Muscle samples were homogenized in 0·05 mol/l phosphate buffer (pH 6·0) and centrifuged at 20 000 *g* for 15 min (4°C). The supernatant containing water-soluble heme proteins, which have pseudoperoxidase activity, was discarded The insoluble pellet was rehomogenized in ice-cold 0·05 mol/l phosphate buffer (pH 6 0) containing 0·5 per cent hexadecyltrimethylammonium bromide and the homogenate sonicated (30 s) in an ice bath, taken through four cycles of freeze and thaw, further sonicated (30 s) and then centrifuged at 40 000 *g* for 30 min (4°C). The supernatant was collected and myeloperoxidase activity assayed spectrophotometrically by measuring the initial change in absorbance (460 nm) resulting from the decomposition of hydrogen peroxide in the presence of *o*-dianisidine. The results are expressed as change in absorbance units min^{-1} g wet muscle $weight^{-1}$

Gastrocnemius muscle viability

This was assessed in the gastrocnemius muscles harvested at the conclusion of each experiment in normal rats ($n = 10$), controls ($n = 10$) and animals given anti-Mac-1 ($n = 10$) using a previously

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described technique employing the histochemical stain nitroblue tetrazolium[12]. Percentage viability was quantified in coronal sections of the muscle by computerized planimetry.

Gastrocnemius muscle oedema

In a further series of experiments, both gastrocnemius muscles were harvested from normal rats ($n = 10$), controls ($n = 10$) and monoclonal antibody-treated animals ($n = 10$). The muscles were weighed (wet weight) and then dried at 80°C in a convection oven for 48 h and reweighed (dry weight). Muscle oedema was quantified by calculating the wet : dry weight ratio in each limb. No correction was made for the haemoglobin content of the muscles as perfusion in normal and anti-Mac-1 treated animals was similar, making it unlikely that changes in wet weight in treated animals reflects alteration in flow.

Gastrocnemius muscle perfusion

Microvascular muscle perfusion after tourniquet release was quantified (normal: $n = 9$, control: $n = 9$, anti-Mac-1 treated: $n = 9$) with laser Doppler flowmetry (Array; Oxford Optronics, Oxford, UK). Immediately before tourniquet release a small area of skin was removed to expose the medial head of the gastrocnemius muscle in both the study limb and the contralateral normal limb. Specially designed laser Doppler probes were placed on the muscle surface and held in position with a double-sided adhesive ring. Incorporated within each probe were three sets of photo-detecting fibres which allowed microvascular perfusion to be measured from three different sites. The signal received from each of the photo-detectors was processed to calculate a numerical estimate of microvascular perfusion, which was recorded in arbitrary blood perfusion units. Mean muscle perfusion was then calculated for each limb at 10, 120 and 240 min of reperfusion in the control and anti-Mac-1 groups, and at equivalent time points in normal rats.

Statistical analysis

Comparison between groups was peformed using the Mann–Whitney *U* test with $P < 0{\cdot}05$ indicating significance.

Results

Myeloperoxidase

Gastrocnemius myeloperoxidase levels were significantly increased in the reperfused limb of control animals compared with those in normal rats (*Table 1*). However, in animals given anti-Mac-1 antibody, muscle myeloperoxidase was barely detectable after revascularization and was no different from that in rats given a general anaesthetic alone (normal levels). These results suggest that postischaemic skeletal muscle reperfusion is associated with marked neutrophil sequestration which is abolished by the administration of anti-Mac-1 monoclonal antibody.

Table 1 Gastrocnemius myeloperoxidase activity, muscle viability and muscle oedema in experimental limbs of normal and control rats, and animals treated with anti-Mac-1 monoclonal antibody

	Myeloperoxidase (units min^{-1} g wet tissue^{-1})	Viability (%)	Oedema (wet : dry weight)
Normal	0·05 (0·0–0·1)	100 (100–100)	3·98 (3·92–4·02)
Control	2·95 (1·72–4·65)*	53 (33–61)*	6·31 (5·18–6·79)*
Anti-Mac-1	0·025 (0·0–0·1)‡	95 (68–100)†	5·90 (5·36–7·39)*

Values are median (interquartile range). *$P < 0{\cdot}001$ *versus* normal; †$P < 0{\cdot}01$ *versus* control, not significant *versus* normal; ‡$P < 0{\cdot}001$ *versus* control, not significant *versus* normal (Mann–Whitney *U* test)

Gastrocnemius muscle viability

In normal animals there was no evidence of muscle necrosis, confirming that the duration of the experiment had no detrimental effect upon muscle viability (*Table 1*). By comparison, all control animals showed evidence of muscle necrosis in the reperfused limb, with a median percentage muscle viability of 53 per cent. In contrast, muscle viability was preserved in rats given the anti-Mac-1 monoclonal antibody (median viability 95 per cent).

Gastrocnemius muscle oedema

Although normal animals did not develop muscle oedema, significant swelling occurred after 6-h ischaemia and 4-h reperfusion in control rats (*Table 1*). This was not ameliorated by administration of anti-Mac-1 monoclonal antibody.

Gastrocnemius muscle perfusion

In normal animals, muscle perfusion remained constant for the duration of the experiment, while control animals showed impaired reflow throughout reperfusion (*Table 2*). In rats receiving the anti-Mac-1 monoclonal antibody, muscle perfusion was impaired at 10 min (not significantly different from controls) but subsequently returned to normal after 120 and 240 min of reperfusion.

Non-ischaemic limbs

Gastrocnemius muscle viability, oedema and perfusion measured in the contralateral normal limbs of control and anti-Mac-1-treated animals were no different to those observed in the limbs of normal animals.

Table 2 Microvascular blood flow in the gastrocnemius muscle during reperfusion

	Arbitrary blood perfusion units at		
	10 min	120 min	240 min
Normal	126 (106–178)	147 (71–179)	115 (95–267)
Control	4 (0–16)*	29 (22–43)†	19 (6–31)†
Anti-Mac-1	0 (0–10)*	145 (31–165)‡	107 (48–177)§

Values are median (interquartile range). *$P < 0{\cdot}001$ *versus* normal; †$P < 0{\cdot}005$ *versus* normal; ‡$P < 0{\cdot}05$ *versus* control, not significant *versus* normal; §$P < 0{\cdot}001$ *versus* control, not significant *versus* normal (Mann–Whitney *U* test)

Discussion

Skeletal muscle reperfusion injury undoubtedly contributes to the failure of limb salvage after technically successful surgery for acute limb ischaemia[1,3,15]. Pharmacological modification of the biochemical and cellular events which promote this injury may reduce the need for limb amputation and might also be expected to ameliorate the remote organ effects of such injury. During reperfusion oxygen free radical release results in the synthesis of lipid mediators (thromboxane A_2, leucotriene

B_4) and chemotactic peptides (complement component C5a), which promote neutrophil activation and chemotaxis[2,5,6]. Neutrophils may initiate further local tissue injury after transmigration into the reperfused muscle[8,9].

These events require neutrophil binding to the microvascular endothelium and this adhesive interaction is mediated by specific glycoproteins on the surface of neutrophils and corresponding endothelial receptors. This ligand mechanism appears to be mediated by the neutrophil glycoprotein complex CD11/CD18 after chemotactic stimulation[10,11]. CD11/CD18 is a family of heterodimers which share the same common β_2 chain (CD18) covalently linked to one of three different α chains (CD11a, CD11b or CD11c). The CD11b/CD18 or Mac-1 receptor is rapidly upregulated on the neutrophil cell surface after activation[11] and is thought to promote rapid neutrophil adhesion to the endothelium[10,11]. Mac-1 is also required for adhesion-dependent release of destructive oxygen free radicals and proteolytic enzymes[10,16,17].

In the present study administration of anti-Mac-1 monoclonal antibody before reperfusion prevented the marked neutrophil sequestration (myeloperoxidase content) within the reperfused muscle which occurred in untreated control animals. Simultaneously, it was noted that anti-Mac-1 antibody administration did not affect the circulating neutrophil count and its effect can be assumed to be the result of specific inhibition of the Mac-1 receptor. However, these experiments do not indicate whether the reduction in muscle myeloperoxidase levels in treated animals is the result of inhibition of neutrophil adhesion, endothelial transmigration, or both, as these events may be similarly dependent on the Mac-1 integrin[18].

In control animals a persistent reduction in microvascular blood flow (laser Doppler flowmetry) in the gastrocnemius muscle was observed during reperfusion, confirming the authors' previous findings using radioisotope techniques[12]. In the present study, early muscle perfusion (10 min) was impaired in both control rats and those given anti-Mac-1 monoclonal antibody and it can be concluded that this occurs independently of any events mediated by the Mac-1 receptor. Possible causes of initial low reflow include passive capillary plugging by neutrophils, release of the potent vasoconstrictor thromboxane A_2 during reperfusion[19] or the superoxide-dependent annihilation of endothelial-derived relaxing factor[20]. However, after 120 and 240 min of reperfusion microvascular blood flow improved significantly in animals given anti-Mac-1 antibody, suggesting that the reduced perfusion observed in control animals at these time points is neutrophil dependent.

Neutrophils may impair capillary perfusion by several mechanisms during revascularization. They become less deformable after activation and this may lead to passive capillary obstruction[21]. Alternatively, neutrophil–endothelial adhesion may lead to permanent capillary occlusion[21]. Both the latter and neutrophil aggregation, which may cause further mechanical occlusion, are Mac-1-dependent events.

The anti-Mac-1 monoclonal antibody also substantially reduced muscle necrosis in these experiments, although the precise mechanism by which this was achieved is not clear. It is likely that inhibition of neutrophil sequestration, reducing local production of oxygen free radicals and proteolytic enzymes, was an important factor. Furthermore, improved muscle perfusion and thus oxygen and nutrient delivery to the tissues may also be relevant.

Previous work by Carden *et al.*[22] has demonstrated a role for an anti-CD18 antigen in ameliorating skeletal muscle reperfusion injury in an isolated canine gracilis preparation. Such a model may not be representative of events after whole-limb ischaemia and so the findings of the present study are of some importance

Although muscle blood flow and viability were returned to normal in rats given anti-Mac-1 antibody, muscle oedema still occurred. Its development, despite preventing neutrophil recruitment into the reperfused muscle (myeloperoxidase content), confirms that neutrophil transmigration is not the only mechanism which may promote postischaemic muscle oedema, and is consistent with previous reports[2,23]. Furthermore, reperfusion oedema may occur in models using a neutrophil-free perfusate[24]. While this might be explained by an increase in endothelial permeability after depletion of intracellular adenosine triphosphate levels during the period of ischaemia[25], endothelial production of oxygen free radicals[26] and vasoactive eicosanoids[19] during reperfusion may also be a factor. The pathogenesis of reperfusion oedema, therefore, requires further investigation.

In summary, this study demonstrates that an anti-Mac-1 monoclonal antibody can prevent neutrophil recruitment, improve postischaemic muscle perfusion and reduce muscle necrosis after hindlimb ischaemia and reperfusion. These findings are consistent with recent reports in which the administration of anti-CD18 monoclonal antibodies have similarly improved muscle viability[23] and reduced pulmonary oedema (remote organ injury) after lower-limb revascularization[27]. While there may be some concern that an anti-Mac-1 monoclonal antibody might produce a syndrome mimicking a leucocyte adhesion molecule deficiency state (characterized by recurrent sepsis), evidence from previous animal studies has failed to confirm that this is the case[28,29] and so inhibition of endothelial–neutrophil adhesion might have a role in the prevention of skeletal muscle reperfusion injury.

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The prevalence of chronic lower-limb ulceration has been underestimated: results of a validated population questionnaire

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A validated population questionnaire was used to survey 12 000 randomly selected inhabitants, aged 50–89 years, in two defined regions of Sweden. The sample included 7 per cent of the total population in the age interval. Overall response rate was 91 per cent. Open ulcers were reported by 306 subjects and 143 (47 per cent) agreed to be examined. The false-positive response rate was high (43 per cent). The observed point prevalence of open leg ulcers was 0·63 (95 per cent confidence interval 0·54–0·72) per cent of the total population. The overall prevalence of leg ulcer history (open plus healed) in the population was estimated to be around 2 per cent and the ratio of open:previous ulcers was 1:2. This study shows a point prevalence more than double that expected, indicating a high rate of self treatment. Assessments of leg ulcer prevalence through the health care system, without knowledge of the rate of self care, measure only the workload of health care professionals. The problem of leg ulcers has generally been underestimated.

Leg ulcers form a common problem and are estimated to affect 1 per cent of the adult population[1]. At any time 0·1–0·3 per cent of the total population in Western countries has been estimated to have an open leg ulcer (foot ulcers included)[1–3]. These data are derived from studies mainly assessing patients with leg ulcers known to health care professionals. It is unknown to what extent people are taking care of leg ulcers without professional help. Therefore, the true prevalence of leg ulcers in the population remains unknown. A knowledge of the true size of the problem is vital if an improvement in the care of patients with leg ulcer is to be achieved, and to define risk factors.

To assess the true point prevalence of chronic leg ulceration in the community a postal questionnaire was sent to a random sample of the population in two defined regions in Sweden, the city of Malmö and the county of Skaraborg. A major city and a mixed urban and rural county were chosen to allow detection of any geographical difference in prevalence.

Methods

A postal questionnaire was sent to 12 000 randomly selected persons, aged 50–89 years; 6000 in the city of Malmö (population 232 908) and 6000 in the county of Skaraborg (population 274 545) (*Fig 1*). The sample included 7 per cent of the total population in the age interval The sample size and the age interval were based on the results of a previous cross-sectional survey in Skaraborg county[2]. Using this size of sample it was expected to find at least 100 persons with open leg ulcers, 50 in each area. The sample was randomly selected by computer using official population registers (Malmö datacentral and Lansstyrelsen i Skaraborgs lan, 2 January 1990).

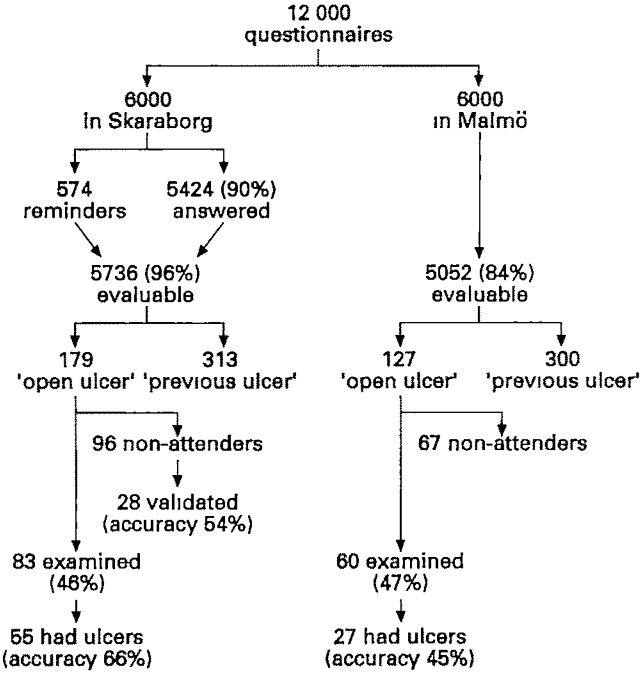

Fig. 1 Flowchart of the study

The postal questionnaire was easy to understand and to complete. It contained a short introduction presenting the purpose of the study and a definition of a 'leg ulcer' as 'any wound below the knee (including the foot) that did not heal within a 6-week period after onset of ulceration, regardless of the cause of the ulcer'. Two questions were asked: (1) Do you have an open leg ulcer now? (2) Have you ever had a leg ulcer? Those who responded 'Yes' to either of these questions were asked to mark the location of the ulcer on a drawing of two legs, to reduce the risk of false-positive responses[4]. If a location was not marked the answer was considered not evaluable. The questionnaire was tested in a pilot study on 20 patients with known leg ulcers and 20 age- and sex-matched controls All controls answered correctly. Two patients with known ulcers did not respond despite one reminder. An additional two had died and one had moved The remaining 15 answered correctly.

The questionnaires were sent out during a 6-week period (February–March 1990) A reminder was sent to non-responders in Skaraborg but not in Malmö. All those who stated they had an open leg ulcer were invited to a clinical examination, to validate the leg ulcer disease and to assess the aetiology. All were evaluated by the same observer (O.N.). A standardized examination was performed as used previously in the Skaraborg study[5,6], and causes of the ulcers were classified according to

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Table 1 Response rate

	Population in age interval	Questionnaire returned	Not found	Dead	Non-responders*	Response rate (%)†
Malmo	87 777	5075 of 6000	24	22	902	85
Skaraborg	90 616	5745 of 6000	17	17	230	96
Total	178 393	10 820 of 12 000	41	39	1132	91

*Non-evaluable subjects included; †people not found or dead are excluded

Table 2 Causes of false-positive responses

	No of people
Eczema	46 (75)
Ulcer healed in less than 6 weeks	3 (5)
Previous ulcer only	1 (2)
Psoriasis	2 (3)
Verruca vulgaris	1 (2)
No skin disorder	8 (13)

Values in parentheses are percentages

Table 3 Aetiological classification of leg ulcers in 95 legs of 82 patients

Aetiological group*	No. of legs	Expected percentage*
Venous	35 (37)	(40)
Mixed *venous* and arterial†	9 (9)	(14)
Mixed *arterial* and venous†	4 (4)	(4)
Arterial	0 (0)	(7)
Arterial and diabetic (neuroischaemic)	9 (9)	(9)
Diabetic (neuropathic)	12 (13)	(4)
Pure traumatic	3 (3)	(2)
Pressure-induced	9 (9)	(3)
Multifactorial (combined arterial, venous and diabetic)	2 (2)	(3)
Other multifactorial	5 (5)	(7)
Other single causes	7 (7)	(6)

Values in parentheses are percentages. *According to Nelzén *et al*[5]; †italicized factor dominating.

Nelzén *et al.*[5]. The accuracy of responses among those who were unwilling to attend the examination was evaluated using a random sample of 28 non-attenders in Skaraborg county, by assessing medical records and making inquiries of district nurses to validate the answers

Based on the epidemiology study performed previously in Skaraborg county[2,6], 90 per cent of patients with leg ulcer were expected to be found in the 50–89-year age group. Thus, to be able to estimate the point prevalence in the total population in the present study it was assumed that 10 per cent of patients with leg ulcer were either older or younger than the age group studied. To estimate the overall prevalence of leg ulcer history it was assumed that the accuracy of positive responses among people with only a previous history of ulcers was similar to that of those reporting open leg ulcers

The study was approved of by the ethics committees at the Universities of Lund and Gothenburg.

Statistical analysis

In the analysis efforts were concentrated on not overestimating leg ulcer point prevalence. The point prevalence of leg ulcer was calculated, based on responders in each area and age decade. It was then extrapolated to estimate the point prevalence in the total population. Prevalence figures were given as observed, assuming an equal accuracy of response among non-attenders, based on the sample validated in Skaraborg county. Confidence intervals (c.i.s) were calculated at 95 per cent level of certainty.

Results

Some 90 per cent of all questionnaires were returned (*Table 1*). The primary response rate was 90 per cent in Skaraborg and 84 per cent in Malmö. After one reminder the response rate in Skaraborg rose to 96 per cent. There were a total of 10 788 evaluable questionnaires. The overall response rate was 91 per cent; 5736 evaluable in Skaraborg and 5052 in Malmö (persons not found or reported dead excluded). Open leg ulcers were reported by 306 persons and previous ulcers by 613.

Response accuracy

In all, 143 of 306 people reporting open ulcers (47 per cent) were examined; 163 declined the offer to attend for assessment. In 82 of 143 examined, leg ulcers were verified, giving a true positive response rate of 57 per cent. The rate was lower in the city of Malmö (45 per cent) than in the county of Skaraborg (66 per cent). Causes of false-positive responses are listed in *Table 2*.

Among a randomly selected sample of 28 non-attenders from Skaraborg county who had reported open ulcers, leg ulcers known to health care professionals were verified in 15 (54 per cent).

Patients with leg ulcer

There were 82 patients examined with proven leg ulcers in 95 legs; 38 men and 44 women. Median (range) age was 71 (50–89) years. One-third of the patients (27) had diabetes. Almost one-quarter (24 per cent) of all ulcers were located at the foot.

Aetiology

Ulcer aetiology is shown in *Table 3*. With two exceptions the aetiological distribution was close to the expected: pure arterial ulcers were not found and diabetic neuropathic ulcers were over-represented in the sample. In 16 per cent of ulcerated limbs arterial and venous insufficiency co-existed. A major venous cause was present for 46 per cent of ulcers and 13 per cent had a possible dominating ischaemic component. Of 44 venous ulcers (aetiological groups venous, mixed *venous* and arterial) 18 were caused solely by varicose veins (isolated superficial venous incompetence); the remainder were due to deep venous insufficiency (reflux in the popliteal vein).

Table 4 Age-specific point prevalence of open leg ulcer

Age (years)	Population	No. of questionnaires returned	No. of ulcers examined	No. of ulcers calculated in sample	Observed prevalence (%)	Expected prevalence (%)*
50–59	53 089	2890	13	27	0·9	0·1
60–69	57 127	3140	27	48	1·5	0·4
70–79	46 310	2795	22	43	1·5	1·3
80–89	21 867	1995	20	63	3·2	2·8

*Based on patients known to health carers[2,6]

Ulcer care

In 36 of 82 cases (44 per cent) self care was used for ulcer dressing, in 31 of 36 without regular professional supervision (38 per cent of all). The proportion was even higher, 13 of 19, for people below retirement age (65 years); only two of 13 had professional supervision.

Leg ulcer prevalence

The observed total point prevalence of open leg ulcers was 0·63 (95 per cent c.i. 0·54–0·72) per cent, more than double that expected. The age-specific point prevalence figures are substantially higher than expected in the two youngest age decades studied (*Table 4*). There was a higher point prevalence of leg ulcers in Skaraborg, indicating a true geographical difference (Skaraborg 0·77 (95 per cent c.i. 0·64–0·80) *versus* Malmö 0·46 (95 per cent c.i. 0·34–0·58) per cent).

Assuming that people who reported having had ulcers previously had the same response accuracy as those reporting open ulcers, the ratio of open : previous leg ulcers was 1 : 2, giving an overall prevalence of leg ulcer history (open plus healed) of 1·8 per cent in the total population and 2·1 per cent in the adult population above the age of 15.

Discussion

This study is the first to estimate the true point prevalence of leg ulcers in the population. Compared with results from previous cross-sectional studies performed in the same geographical areas[2,7] and in other countries[1,3] an unexpectedly high point prevalence of open leg ulcers was found. In Skaraborg county in 1988 the point prevalence of leg ulcers known to health care professionals was 0·30 per cent[2]. In Malmö in 1990 Lindholm *et al.*[7] observed a prevalence of 0·12 per cent. The combined point prevalence found in the present study was 0·63 per cent, at least twice as high. This estimate is based on careful interpretation of the observed prevalences, using the lower limits of the confidence intervals, in order to minimize the risk of overestimating the size of the problem. Therefore, the true prevalence might be even higher. Regardless of the exact figures, this study indicates that probably half of all patients with leg ulcer are unknown to health care professionals.

Self treatment, without regular professional supervision, was applied by 38 per cent of those examined in this study, despite most of them being elderly. However, 68 per cent of those below retirement age were self caring and only two of 13 received professional supervision. A higher proportion of self treatment could be expected among people who did not attend the examination. In view of these results, one might question the validity of most previous point prevalence estimates from cross-sectional studies.

For ethical reasons each person invited to attend for clinical examination was allowed a free choice to participate or not. This was one reason why it was not possible to examine more than 47 per cent of all people approached. Another reason was that individuals were not visited in their own homes or in hospitals, and so patients with restricted mobility might have had difficulty in attending. To cover the uncertainty caused by the relatively low proportion of patients actually examined the accuracy of responses was validated in a random sample of non-attenders. In that sample, current leg ulcer disease known to health care professionals was verified for just over half, indicating a similar response accuracy among non-attenders, assuming an appropriate proportion are unknown to health carers.

Point prevalences of leg ulcers known to health carers in Sweden are among the highest reported[1,2,8], but this does not necessarily mean that the problem of leg ulcers is greater than that in other countries. It may merely reflect the tendency and ability to seek professional care. Although people in the UK[1] and Australia[3] also have a system of universal health cover, there might be other factors that influence the tendency to seek professional help. Age, tradition, accessibility, costs for visits to district nurses or doctors and additional costs for travel might be relevant. In countries with other health insurance systems or less developed or less accessible primary care, one might expect higher proportions of self care than were found here. Unless the rate of self treatment is estimated, point prevalence of leg ulcers describes only the workload for health care professionals.

The geographical differences in prevalence between the city of Malmö and the county of Skaraborg were expected from previously published studies[2,7]. Direct geographical comparisons based on present results should, however, be performed with some care because of the higher number of non-responders in Malmo. Geographical differences are also likely to exist between different countries, especially with respect to age distribution, but the question is — on what level?

It is commonly cited that 1 per cent of the adult population suffers from leg ulcers[1]. This value is derived from the Klatov study by Bobek *et al.*[9] and the Basle study by Widmer[10]. Both studies registered only people with a history of 'presumed venous ulcers'. The Stockbridge study in Scotland by Dale *et al.*[4] seemed to confirm that 1 per cent of the adult population (aged above 15 years) had had leg ulcers at some time. However, this was a limited survey based on a small sample of 549 selected elderly patients (aged 65 years or more) drawn from general practitioners. These data were used to estimate the prevalence in the general population by referring to data from the Lothian and Forth Valley Study[11], which was conducted by the same group, although in the latter forefoot ulcers were excluded[1]; the studies therefore had different definitions of 'a leg ulcer'. Only patients known to health care professionals were included in the latter series. By comparing the data from the two studies it was estimated that one of five patients with a history of leg ulcer have open ulcers at any one time. Since patients with chronic forefoot ulcers were excluded and the assessment in the general population was restricted to elderly people, the overall prevalence of chronic lower-limb ulceration must have been underestimated. In the present study the overall prevalence of leg ulcers (open plus healed) was 2·1 per cent in the adult population and one of three with an ulcer history had open ulcers at any one time. These data are based on a large scale population questionnaire, including individuals below retirement age with all types of chronic ulcer, and ought to be more representative. The data are supported by results from surveys on selected populations where the overall prevalence was high[12,13] and by the high prevalence of leg ulcer history (2·7 per cent in adults aged over 15 years) observed in the Tubingen study by Fischer[14]. Provided the aetiological spectrum is similar among patients with previously healed ulcers, the data also support the overall prevalence of venous ulcers of 1 per cent reported from Czechoslovakia[9] and Switzerland[10].

Using a population questionnaire sent to 6 per cent of all people aged 65 years or older in Gothenburg, Andersson *et al.*[15] reported the point prevalence of leg ulcers of vascular cause to be 1·02 per cent in the sample. This was within the expected range[8], indicating that most elderly patients with leg ulcer are known to health carers. This was also the finding in the present study where the age-specific prevalence was close to that expected for the older age decades (*Table 4*). In the two younger decades, however, substantially higher prevalences than expected were demonstrated. The assumption that younger people to a greater extent take care of their ulcers themselves seems reasonable.

The aetiological distribution showed the expected pattern (*Table 3*) indicating that the sample was representative. The proportion of foot ulcers was similar and the prevalence of diabetes was high, as in the Skaraborg study[5,16].

The high rate of self treatment found in this study is remarkable, especially since it seems to be most commonly adopted by people below retirement age. This might delay or prevent effective treatment from being used in a large group of people, at a time when their ulcers and the causative factors are more easily curable. It is important to detect people with leg ulcers early, in order to find those with curable causes of the ulcers, such as varicose veins. Since these people are not always known to health care professionals, more information directed at the public is necessary. Because self treatment is common, the true point prevalence of open leg ulcers has generally been underestimated.

Acknowledgements

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Time-dependent histamine release from stored human blood products

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Perioperative tranfusion of whole blood has been shown to amplify trauma-induced immunosuppression, which could be attenuated by perioperative administration of histamine$_2$ receptor antagonists. Supernatants from different blood products were, therefore, analysed for histamine content during storage. Whole blood (six units), plasma-reduced whole blood (six units), and plasma- and buffy coat-reduced (saline-adenine-glucose-mannitol) (SAGM) blood (six units) from unpaid healthy donors were stored in the blood bank for 35 days at 4°C. Plasma histamine and total cell-bound histamine content at donation, and histamine concentration in samples drawn from the units on days 0, 2, 5, 9, 14, 21, 28 and 35 were analysed with an enzyme-linked immunosorbent assay. Median plasma histamine concentration was 4·8 (range 1·9–14·3) nmol/l ($n = 18$). Median total cell-bound histamine content was 417·0 (range 176·0–910·0) nmol/l in whole blood and 475·0 (range 360·0–1560·0) nmol/l in plasma-reduced whole blood, while it was undetectable in SAGM blood. Spontaneous histamine release increased in a time-dependent manner from a median of 6·7 (range 2·2–17·4) nmol/l at the time of storage to 175·0 (range 33·0–485·0) nmol/l at day 35 in whole blood, from 18·8 (range 8·2–38·5) to 328·5 (range 224·0–1137·0) nmol/l in plasma-reduced whole blood, and from 0·5 (range 0·5–1·5) to 2.2 (range 1·4–6·9) nmol/l in SAGM blood. These results show spontaneous histamine release during storage of human blood products which contain full amount of leucocytes, and this may play a significant role in detrimental effects of blood transfusion.

Perioperative allogeneic blood transfusion may increase the risk of postoperative infectious complications[1] and reduce recurrence-free and long-term survival rates after curative surgery for malignancy[1]. These potential detrimental effects of blood transfusion may be mediated via immunosuppressive effects[1–3]. Major trauma and/or surgery induce transient immunosuppression, which may be related to subsequent development of postoperative infectious complications[4,5] and cancer recurrence[5]. Perioperative blood transfusion appears to amplify trauma-induced immunosuppression[2,6] and may thereby enhance these effects[2,7]. The mechanisms of mediation have not been fully characterized, but donor leucocyte antigens and plasma components may be involved[2,7,8]. It was suggested that donation of autologous blood 5–10 days before elective operations would reduce allogeneic effects. Results from studies of elective cancer surgery, however, comparing allogeneic and preoperative donated autologous blood showed similar high cancer recurrence rates in all transfused patients[9,10].

Plasma from patients undergoing elective surgery for colorectal cancer and receiving intraoperative allogeneic blood transfusion induces a significant increase in mitogenic activity of fibroblasts in culture compared with plasma from those having no blood transfusion[11]. This mitogenic activity correlated with storage time of the transfused blood, suggesting a release of 'growth' factors during storage[11]. Histamine is a well known potent mitogenic and proliferative factor in normal and cancer tissue[12] and an immunomodulator[13]. The histamine$_2$ (H$_2$) receptor antagonist ranitidine reduces postoperative transfusion-induced immunosuppression by whole blood[14]. The purpose of the present study, therefore, was to evaluate a possible time-dependent histamine release from different human blood products during storage.

Materials and methods

Peripheral venous blood (4·5 ml) was drawn from 18 unpaid, healthy and randomly selected blood donors into endotoxin-free tubes (Becton Dickinson, Mountain View, California, USA) containing 0 5 ml sodium citrate (0·129 mol/l) and aprotinin (12·5 µl/ml), and kept on ice. Sodium citrate was used as anticoagulant because of histamine contamination of heparin preparations[15] and because sodium citrate is used in standard blood bags. The plasma was separated from the cells and frozen at − 80°C until use. One unit of blood (450 ml) was drawn from each of the 18 donors under standard conditions into blood bags containing 63 ml citrate, phosphate, dextrose and adenine solution as anticoagulant. The 18 units of donated blood were prepared as follows. six units of plasma-reduced whole blood were produced by removing 200 ml plasma from each unit; six units of SAGM (saline-adenine-glucose-mannitol) blood were produced by centrifugation of six units of whole blood at 5000 G for 10 min and removal of plasma and buffy coat, and subsequent addition of 100 ml SAGM solution. The standard reduction of leucocytes in SAGM blood is 65–75 per cent. The remaining six units of whole blood, the six units of plasma-reduced whole blood and six units of SAGM blood were stored in the blood bank under standard conditions for 35 days at 4°C. As soon as the stored blood units were cooled to 4°C, 4·5 ml blood was drawn on ice from each unit in endotoxin-free plastic tubes (Becton Dickinson) for analysis of total cell-bound histamine content. Samples were drawn from all units on days 0, 2, 5, 9, 14, 21, 28 and 35 after storage for analysis of spontaneous histamine release.

SAGM blood is the standard blood product for transfusion in Denmark, and 4·5 ml blood was drawn on ice from 56 randomly selected units of this product immediately before clinical transfusion. It was ensured that these units were handled as scheduled for transfusion, i.e. kept at room temperature and manipulated to mix cells and SAGM solution.

Some 50 µl of the blood for analysis of total cell-bound histamine content was diluted in 950 µl sterile water (dilution 1:20). The samples were then frozen and thawed twice, and frozen at − 80°C until analysis. Blood for analysis of histamine concentration in stored and transfused units was centrifuged at 4°C at 1200 G for 10 min and the supernatants were frozen at − 80°C until use.

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Table 1 Time-dependent spontaneous histamine release from stored blood

	SAGM blood (six units)	Plasma reduced whole blood (six units)	Whole blood (six units)
Total cell content	n.d.	475·0 (360·0–1560·0)	417·0 (176·0–910·0)
Day 0	0·5 (0·5–1·5)	18·8 (8·2–38·5)*	6·7 (2·2–17·4)
Day 2	0·6 (0·5–2·2)	11·4 (9·2–23·0)	7·4 (2·8–15·0)
Day 5	0·8 (0·5–2·4)	19·9 (12·5–45·0)*	8·2 (3·0–23·0)
Day 9	1·5 (0·5–3·3)	29·0 (15·9–130·0)*	14·2 (7·2–32·0)
Day 14	1·7 (0·5–4·3)	34·8 (29·0–180·0)*	21·0 (6·2–50·0)
Day 21	1·7 (1·0–3·8)	79·0 (63·0–385·0)*	50·8 (13·5–181·0)
Day 28	2·2 (1·5–5·6)	196·5 (128·0–763·0)*	108·0 (21·0–385·0)
Day 35	2·2 (1·4–6·9)	328·5 (224·0–1137·0)*	175·0 (33·0–485·0)

Values are median (range) nmol/l. *$P < 0{\cdot}05$ (plasma-reduced whole blood *versus* whole blood). SAGM, saline-adenine-glucose-mannitol; n.d., not detected

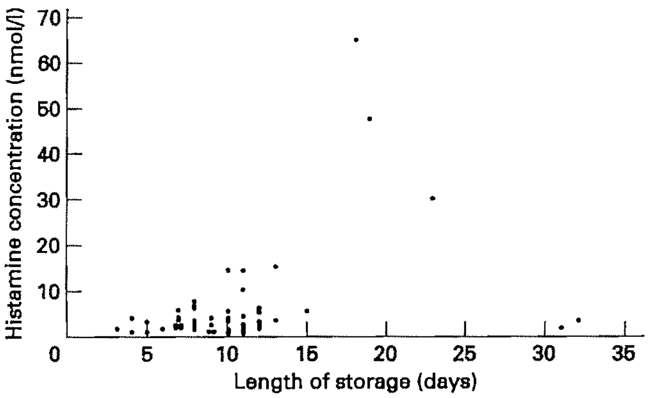

Fig. 1 Histamine concentration in 56 randomly selected units of saline-adenine-glucose-mannitol blood. Samples were drawn immediately before clinical transfusion

Plasma histamine, total cell-bound histamine content and spontaneous histamine release were analysed with a commercially available enzyme-linked immunosorbent assay (Immunotech, Marseille, France). Detection limit was 0·5 nmol/l and all analyses were performed in duplicate.

Descriptive statistical analysis, the Wilcoxon rank sum test and the Mann–Whitney *U* test were used to evaluate the results. Values are given as median (range). $P < 0{\cdot}05$ was considered significantly different.

Results

The median plasma histamine level in the 18 donors was 4·8 (range 1·9–14.3) nmol/l. The total cell-bound histamine content was 417·0 (176·0–910·0) nmol/l in whole blood and 475·0 (360·0–1560·0) nmol/l in plasma-reduced whole blood ($P > 0{\cdot}2$) (*Table 1*). The total cell-bound histamine content was undetectable in SAGM blood.

The histamine concentration (spontaneous release) increased during storage of SAGM blood from 0·5 (0·5–1·5) nmol/l on day 0 to 2·2 (1·4–6·9) nmol/l on day 35 ($P < 0{\cdot}05$) (*Table 1*). Analysis of the 56 random samples from SAGM blood collected immediately before transfusion showed a significant concentration of free histamine in seven units stored for between 10 and 23 days (*Fig. 1*). This observation appeared independent of storage time, because two units stored for 31 and 32 days respectively had a histamine concentration comparable with that in plasma.

The histamine concentration in whole blood and plasma-reduced whole blood units increased from day 0 to day 35 (*Table 1*). The values were significantly ($P < 0{\cdot}05$) higher in plasma-reduced whole blood than in whole blood at all days of analysis except at day 2 (*Table 1*). The percentage of spontaneous histamine release by total cell-bound histamine content also increased significantly in both plasma-reduced whole blood and whole blood, according to values in *Table 1*. When correcting by volume (513 ml in whole blood and 313 ml in plasma-reduced whole blood), however, the content of histamine per unit was no different in the two blood products.

Discussion

Histamine was previously considered as an effector molecule in immediate hypersensitivity responses[16,17], but evidence also suggests it is a potent mediator in the immune regulation acting on specific histamine receptors expressed by immune-competent cells[5,13,18]. Histamine is released from mast cells and basophils immediately after traumatic events[19] and may play a significant role in the inflammatory response[20], in endotoxic shock mediation[21] and in postoperative peritoneal adhesion formation[22]. In addition, H_2 receptor antagonists may reduce post-traumatic immunosuppression[23,24], which further may indicate a role of histamine[18] as a mediator in trauma-induced immunosuppression. Evidence has accumulated that suggests histamine is a mediator of cancer cell proliferation[12,25,26], acting directly via H_2 receptors expressed by tumour cells[27] and/or indirectly by immunosuppression[5]. This is supported by results from treatment of patients with cancer with H_2 receptor antagonists[28–30]. Histamine may play a role in regulation of cardiovascular and central nervous systems[31] and in the coagulation cascade[32].

Transfusion of allogeneic whole blood products leads to immunosuppression in non-surgical patients[3], and amplifies trauma-induced immunosuppression[2,6,14]. This may contribute to cancer occurrence[33], and may lead to detrimental effects in surgery and trauma[1]. Hitherto, these effects have been attributed primarily to alloimmunization induced by antigen determinants expressed by donor leucocytes[1,34], but plasma components may also play a major role[8] dependent on storage time[11,35]. Such components may lead to detrimental effects independently of containment in allogeneic or autologous blood.

This study confirms that histamine is released from whole blood during storage[35], and that plasma-reduced whole blood releases similar amounts of histamine when stored under standard conditions. Exclusively, this is based on similar amounts of leucocytes in these two blood products. SAGM blood did not release significant histamine during storage at 4°C, presumably because of depletion of basophils by removal of the buffy coat during the production process. However, histamine was detected in some SAGM units just before transfusion, presumably dependent on high counts of basophils in some donors, on separation procedure in the blood bank, or because of manipulation and gradual warming before transfusion.

Whether or not histamine released from blood during storage plays a significant role in induction of the well known detrimental effects[1] is unknown. Histamine infusion (1 mg over 20 min) to healthy volunteers, however, induces transient systemic symptoms, such as flush, increased heart rate, and decreased diastolic blood pressure and immunosuppression[18]. Transfusion of blood that contains a significant amount of histamine may participate in transfusion-induced immunosuppression, leucocytosis, fever, infectious complications, and cancer occurrence, recurrence and decreased survival[1].

In conclusion, histamine is released from whole blood products during storage but is rarely detected in SAGM blood. Histamine may play a major role in the detrimental effects of blood transfusion and the time dependency may explain why not all transfused patients are at risk after transfusion. It may be more hazardous to transfuse blood contaminated with histamine to patients with malignancy than to those with benign disease, because plasma histamine may be increased[36] and the activity of enzymes for its metabolism decreased[37,38]. It remains to be shown whether histamine is the only toxic mediator released into blood during storage, and whether the mechanism is by leakage from preformed granules and/or after stimulation by other mediators, released from different cell types. Future research should consider leucocyte filtration performed in the blood bank within the first hours of donation[39–41] to reduce time-dependent histamine release from basophils in allogeneic and autologous blood, and alloimmunization to foreign leucocyte antigens in allogeneic blood.

Acknowledgements

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Case report

Adrenal ganglioneuroma

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Ganglioneuromas are benign, differentiated tumours originating from primordial neural crest cells and situated at one end of a spectrum that includes neuroblastoma and ganglioneuroblastoma[1]. The incidence of ganglioneuromas is unknown but they are frequently associated with von Recklinghausen's disease. Most ganglioneuromas are located in the posterior mediastinum and retroperitoneum. The occurrence of these tumours in the adrenal medulla is less common but presents diagnostic difficulty[1,2]. Adrenal ganglioneuromas occur most commonly in children and young adults. Such patients often present with paraneoplastic symptoms such as diarrhoea and hypertension[3]. Malignant transformation of adrenal ganglioneuromas and tumours of mixed ganglioneuroma and phaeochromocytoma have also been reported[3].

Case reports

A 52-year-old woman presented with a painful mass in the left adrenal gland. She had minimal tenderness in the left renal area and mild hypertension (140/90 mmHg), but laboratory tests were otherwise normal. Computed tomography (CT) showed a non-homogeneous, hypodense left adrenal mass 3 cm in diameter. The left adrenal gland was removed uneventfully. The tumour was firm, grey, well demarcated and encapsulated in an adrenal weighing 15 g. Microscopic examination of the tumour showed that it contained mature ganglion cells intermixed with fascicles of spindle cells. Scattered areas of calcification were also apparent and the diagnosis was ganglioneuroma (*Fig. 1*).

A 50-year-old man was admitted complaining of left hypochondrial pain. Physical examination and hormonal studies were normal, but abdominal CT showed a 5-cm mass in the left adrenal. A left adrenalectomy was performed. The adrenal gland was 25 g in weight with a well demarcated, encapsulated tumour 5 cm in diameter. Under microscopic examination, features of the tumour were similar to those found in the 52-year-old woman.

Finally, a 58-year-old woman was admitted with mild hypertension (170/100 mmHg) and pain in the lumbar region. Physical and laboratory findings were normal except for a left adrenal gland mass 2·5 cm in diameter detected by abdominal CT. Left adrenalectomy was performed. The adrenal gland weighed 20 g and measured 6 × 4 × 1·5 cm. Histopathological examination revealed features similar to those of the other two tumours.

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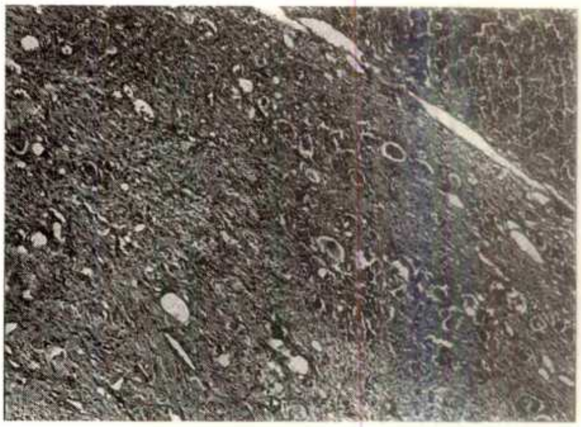

Fig. 1 Microscopic view of ganglioneuroma (original magnification × 80)

Discussion

Ganglioneuromas originate from the medulla in the adrenal gland[1]. The spontaneous maturation of the neuroblastoma to mature ganglioneuroma is recognized[4]; most reported cases of ganglioneuroma are in children and associated with blastoma[2,3]. Furthermore, malignant transformation into malignant peripheral nerve sheath tumours instead of neuroblastoma has been reported[5]. In the three patients reported, multiple sections were studied and no areas of neuroblastoma or other malignant tumour were observed; the ganglioneuromas appear to have occurred *de novo*.

As with neuroblastoma and ganglioneuroblastoma, ganglioneuroma may also secrete catecholamines, and some patients have diarrhoea, hypertension or Cushing's syndrome[1,3].

In the patients described there were no changes that would explain persisting hypertension and no hormonal abnormality was detected. The experience with these patients supports the view that ganglioneuroma can develop spontaneously and asymptomatically[2], and in these patients the diagnosis was coincidental.

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Assessment of the acceptability of conservative management of fibroadenoma of the breast

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A prospective study was performed in 202 patients with 219 fibroadenomas, diagnosed by a combination of clinical examination, ultrasonography and fine-needle aspiration cytology. Patients were given the choice of excision or conservative management with regular monitoring by ultrasonography. Sixteen patients with 18 fibroadenomas opted for excision and all 18 lesions were histologically confirmed as fibroadenomas. A further 152 patients with 163 fibroadenomas were observed for a minimum period of 2 years; 13 fibroadenomas increased significantly in size (all 13 were excised and confirmed histologically as fibroadenomas), 19 decreased significantly in size, 42 resolved and the remaining 89 showed no change in size. Conservative management of fibroadenomas in patients under the age of 40 is safe and acceptable to the majority of women.

Fibroadenomas are benign breast lesions that are considered to be aberrations of normal breast development rather than true neoplasms[1]. It has been routine practice to excise fibroadenomas, but this philosophy is being questioned. A conservative approach would be appropriate providing the lesions can be accurately diagnosed by non-invasive procedures, their natural history has been well defined and this method of management is acceptable to patients.

Using a combination of clinical examination, ultrasonography and fine-needle aspiration cytology (FNAC) it appears possible to identify accurately the majority of fibroadenomas[2]. The present study determined how many patients with fibroadenomas would accept conservative management and defined the natural history of these lesions over a 2-year period in those patients managed by observation.

Patients and methods

Entry into the study was limited initially to patients under the age of 40 with a clinical diagnosis of a single or multiple fibroadenoma(s) measuring 4 cm or less in maximum dimension. Eight patients in their early 40s were included in the study at their own request. Patients underwent breast ultrasonography, mammography if aged 35 years or over and FNAC. Patients with lesions characteristic of a fibroadenoma on clinical, ultrasonographic and cytological (benign sheets of epithelium in a background of bare nuclei) assessment were eligible. A total of 202 patients were enrolled over a 2-year period, 188 with single and 14 with multiple fibroadenomas. The age distribution of patients is shown in *Table 1*. The size range of the fibroadenomas is shown in *Table 2*.

Study protocol

Eligible patients were offered the choice of conservative management with regular assessment of volume by ultrasonography at 3 months, 6 months, 1 year and 2 years or excision under local or general anaesthetic. Options were fully explained to patients who were informed that they could ask for the lesion(s) to be excised at any time during follow-up.

The volume of each fibroadenoma was calculated as previously described[3]. Volumes were monitored by a single individual throughout the study; intraobserver variation was less than 10 per cent[3]. An increase in volume on two sequential ultrasonography measurements of more than 20 per cent in the absence of an identifiable cause such as pregnancy was defined as significant and was considered an indication for excision. A volume decrease of less than 20 per cent on two successive assessments in the absence of factors such as a recent delivery was defined as a significant decrease in volume. Patients with fibroadenomas which decreased in size, resolved or remained the same size were discharged after 2 years. Patients whose fibroadenomas were increasing in size at the 2-year assessment were given a further follow-up appointment.

Table 1 Age distribution of patients

Age (years)	Number of patients
<20	25
20–29	116
30–39	53
>39	8
Total	202

Table 2 Maximum clinical size of fibroadenomas

Size (cm)	Number of patients
<1·0	22
1·0–1·9	116
2·0–2·9	66
3·0–4·0	15

Results

Sixteen patients (7·9 per cent) opted for excision, ten at the time of diagnosis, three during the first 6 months, one between 7 and 12 months and two between the first and second years of observation. Four of the six patients who requested excision did so because they were leaving the area and could not attend for regular follow-up. The 18 lesions removed from these 16 patients were all shown histopathologically to be fibroadenomas.

The remaining 186 patients (92·1 per cent) opted for observation. Thirty-four patients with 38 fibroadenomas defaulted during follow-up, although all but eight attended for at least one follow-up ultrasonographic

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examination and 18 had at least two review appointments. A total of 152 patients with 163 fibroadenomas were monitored for the 2-year study period. Thirteen fibroadenomas (8·0 per cent) increased significantly in size; all 13 were excised and confirmed histologically to be fibroadenomas. Similar numbers of fibroadenomas increased in size during the first and second years of observation. Nineteen (11·6 per cent) decreased significantly in size and 42 (25·8 per cent) resolved, 20 in the first year and 22 during the second or third year. The remaining 89 fibroadenomas showed no change in size.

Over half the patients with fibroadenomas that increased in size (seven of 13) were aged under 20; 28 per cent of all patients in this age group had an increase in size compared with 2·8 per cent in patients 20 years of age or over. There was no difference in the sizes of fibroadenomas which increased in size, when compared with those which remained the same size or got smaller. Of the 15 fibroadenomas over 3 cm in size eight (53 per cent) reduced in size or resolved, compared with 26 per cent of the fibroadenomas less than 3 cm in size. The age distribution of patients whose fibroadenomas got smaller or disappeared did not differ from the age distribution of those patients whose lesions remained static or grew.

One patient, 35 years old, presented at the 6-month review with a new breast mass in the upper outer quadrant (the fibroadenoma had been in the upper inner quadrant). FNAC of the new lesion demonstrated malignant cells and both lesions were excised confirming a fibroadenoma and an 11-mm invasive carcinoma. No other patient was identified as having breast cancer during the study period or following completion of the study (median follow-up 42 months).

Discussion

Although previous studies of the natural history of fibroadenomas have been published, these have used clinical assessment of size, which is unreliable, and inaccurate methods of diagnosis[4–6]. They have also produced conflicting results. Haagensen[4] indicates that fibroadenomas grow to 1–2 cm in size and then stop growing. This view is inconsistent with an Edinburgh study that concluded that the majority of fibroadenomas continue to grow and only 29 per cent remain the same size[5]. In contrast, a South African study reported that 31 per cent of fibroadenomas resolve and another 12 per cent get smaller[6]. The view that some fibroadenomas regress is consistent with the observation that fibroadenomas are found rarely in mastectomy specimens from older patients and in this group the lesions are also less cellular[7].

As the majority of fibroadenomas have a characteristic ultrasonographic appearance, ultrasonography permits identification of fibroadenomas with a greater degree of certainty than is possible by clinical examination alone and allows size and volume to be monitored accurately. Serial examinations in a small selected series of patients with fibroadenomas demonstrated that none of the fibroadenomas changed significantly in size over a 3-year period[2]. The present study, which includes much larger numbers, has demonstrated that over a 2-year period less than one in ten of all fibroadenomas increased in size and more than a third became smaller or resolved.

One concern of leaving a lump in the breast is that a cancer could be missed. By restricting conservative management principally to women under 40 years of age in the present study, the chances of missing a breast cancer have been reduced. Only one patient was identified with a new breast cancer and none of the lesions monitored during the study was shown or has been shown subsequently to be a breast cancer.

Knowledge that few fibroadenomas increase in size is only likely to influence clinical practice if conservative management is acceptable to patients. A survey from South Africa reported that only 21 per cent would opt for conservative management if they developed a further fibroadenoma and only 7 per cent would have preferred to have kept their initial breast lesion rather than have it excised[8]. This contrasts with the findings of a study from Oxford where over 80 per cent of a small group of women with benign breast lumps opted for a conservative approach[9]. The present study supports the Oxford findings with over 90 per cent of patients opting for conservative management. Patients may have been counselled differently or there may be ethnic differences in attitudes to breast lumps.

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Postoperative evaluation of pylorus-preserving gastrectomy for early gastric cancer

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Physical results after pylorus-preserving gastrectomy (PPG) with preservation of the vagus nerve were evaluated. The status of 15 patients with early gastric cancer after PPG was compared with that of 14 patients after distal gastrectomy (DG). The postoperative/preoperative body-weight ratio of the PPG group (0·99) was significantly greater than that of the DG group (0·92). Patients who had PPG had fewer postoperative abdominal symptoms than those who underwent DG. The gastric emptying pattern of patients who had a pylorus-preserving procedure was slower than that of those who had conventional gastrectomy, and more similar to the preoperative pattern. Contraction of the gallbladder after PPG was better than after DG. Gastroscopy revealed that the mucosa of the stomach remnant after PPG was less abnormal than after DG. In conclusion, PPG is a more physiological operation than conventional DG and should be applied in carefully selected cases of early gastric cancer.

Extended gastrectomy with group 2 lymph node dissection (D_2) used to be the treatment of choice for early gastric cancer in Japan[1]. Recently, however, the number of small early gastric cancers detected has increased, and this has led to the frequent application of various limited operations[2,3]. On the condition that radicality should not be compromised, the operative method providing better quality of life should be selected.

Pylorus-preserving gastrectomy (PPG) is one of the limited operations for early gastric cancer, although it was initially designed for and clinically applied to gastric ulcer[4]. Several institutes in Japan have applied PPG in some patients with early gastric cancer. However, postoperative results after PPG have not been assessed in detail. In the present study, the physical status of patients after PPG was evaluated in comparison with that of patients after the conventional operation.

Patients and methods

The 15 patients with early gastric cancer who underwent PPG (PPG group) in this department between March 1992 and April 1993 were ten men and five women, of mean age 57·3 years.

In the PPG procedure, the hepatic and pyloric branches of the vagal nerve were preserved, and the distal part of the stomach was resected while retaining a 1·5-cm pyloric cuff (*Fig. 1*). The reconstruction was performed by a method similar to the Billroth I procedure with gastrogastrostomy using two layers of sutures. In accordance with the Japanese Classification of Gastric Carcinoma[5] issued by the Japanese Research Society for Gastric Cancer group 1 lymph nodes were dissected, but suprapyloric and right cardiac lymph nodes were not. In four patients, group 2 lymph nodes along the left gastric artery, lymph nodes along the common hepatic artery and those around the coeliac artery were also dissected, but the coeliac branch of the vagus nerve was preserved.

Histological examination after operation revealed that all cancerous lesions were confined to the mucosa, and that there was no lymph node metastasis.

Controls were 14 patients with early gastric cancer who underwent conventional distal gastrectomy (DG) with D_2 lymph node dissection in the same period and who had no lymph node metastasis (DG group). There were 11 men and three women of mean age 52·7 years. For patients having DG with D_2 lymph node dissection, the hepatic and pyloric branches of the vagus nerve were completely resected.

In the PPG group, resection of approximately two-thirds of the whole stomach was performed in ten patients and about one-third was resected in five patients. About two-thirds of the stomach was resected in all 14 patients in the DG group. Three patients in each group had a history of gastric ulcer. Two patients in the PPG group had undergone previous cholecystectomy for cholecystolithiasis, and one patient in each group underwent cholecystectomy for cholecystolithiasis during the operation for early gastric cancer. Six patients in the PPG group and four who had DG had epigastric pain before operation, but no patient in either group had previous non-specific gastrointestinal symptoms except one in the DG group who had constipation. Three patients in the DG group and none

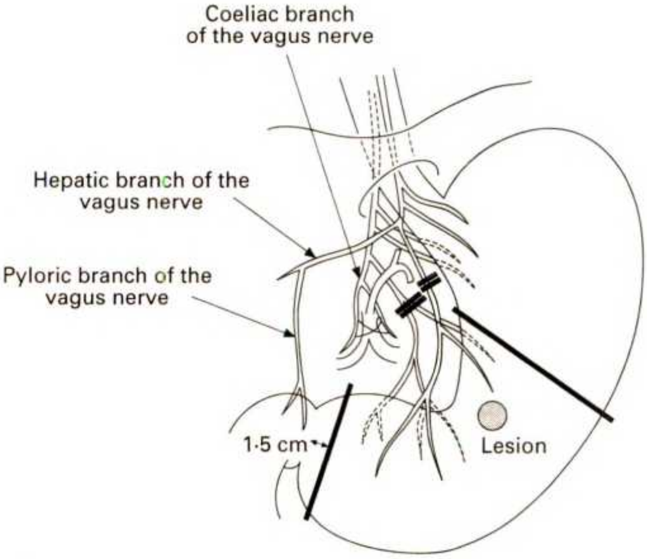
Coeliac branch of the vagus nerve
Hepatic branch of the vagus nerve
Pyloric branch of the vagus nerve
1·5 cm
Lesion

Fig. 1 Pylorus-preserving gastrectomy with preservation of the vagus nerve

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in the PPG group had previous chronic hepatitis. Eight patients in the PPG group and seven in the DG group were smokers. Five patients in the PPG group and four in the DG group drank alcoholic beverages every day. There was no statistical difference between the groups with respect to these parameters (χ^2 test), but a significant difference was detected in the extent of resection by Fisher's direct test ($P = 0{\cdot}04$).

Postoperative follow-up

The items compared 1 year after the operation were as follows.

Body-weight ratio. The postoperative body-weight ratio was calculated as the ratio of postoperative to preoperative body-weight.

Food intake volume and abdominal symptoms. A questionnaire relating to food intake at one sitting and abdominal symptoms after operation was sent to all patients. Concerning the meal, patients indicated the ratio of their present to their preoperative food intake by selecting 1, 2/3, 1/2 or 1/3.

Gastric emptying test by acetaminophen method[6,7]. Acetaminophen is not absorbed in the stomach but is absorbed in the duodenum or jejunum, through which it enters the blood. Patients swallowed an alimentary liquid (200 ml Ensure liquid; Meiji, Tokyo, Japan) containing 1·5 g acetaminophen and serum levels of acetaminophen were measured every 15 min.

Gallbladder contraction test[8]. Before the test, the maximum area of the gallbladder was measured by ultrasonography. The patient then swallowed 200 ml Ensure liquid and the maximum area of the gallbladder was measured every 15 min. Gallbladder contraction rate was calculated as (maximum area before the test − maximum area at a given time)/maximum area before the test.

Gastroscopic findings. Gastroscopy was performed to evaluate the mucosal surface in the stomach remnant. Redness, oedema or erosion of mucosa in the stomach remnant were recorded as in the Sydney System[9]; one point was counted for each feature present, and the sum of the scores was divided by the number of patients in each group (defined as the endoscopic gastritis score).

Statistical analysis

The statistical significance of differences was evaluated by unpaired Student's t test, Fisher's direct test or the χ^2 test, in which two items were compared. $P < 0{\cdot}05$ was considered significant.

Results

Body-weight ratio

The mean(s.d.) postoperative body-weight ratio of the PPG group (0·99(0·07)) was significantly higher than that of the DG group (0·92(0·06)) ($P = 0{\cdot}017$, Student's t test). Among patients who had a pylorus-preserving procedure, there was no significant difference in postoperative body-weight ratio between those who had two-thirds of the stomach resected (1·0(0·08)) and those who had one-third removed (0·95(0·04), $P = 0{\cdot}176$).

Food intake volume and abdominal symptoms

Questionnaire results indicated that the food intake volume of the patients who had PPG was not greater than that of those who had a conventional procedure. Concerning postoperative abdominal symptoms, patients had fewer abdominal symptoms after PPG than DG, although no significant difference was detected. No patient in the PPG group complained of abdominal pain, diarrhoea or borborygmus (*Fig. 2*). In the PPG group, there was no significant difference in food intake volume or postoperative abdominal symptoms between those who had approximately one-third or two-thirds of the stomach resected.

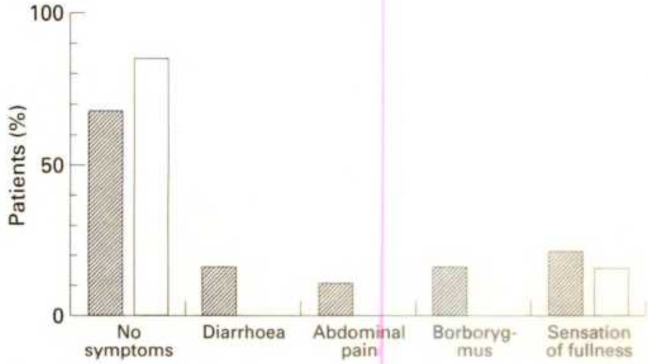

Fig. 2 Abdominal symptoms reported in a questionnaire 1 year after operation in 15 patients who had pylorus-preserving gastrectomy (□) and 14 who underwent distal gastrectomy (▨)

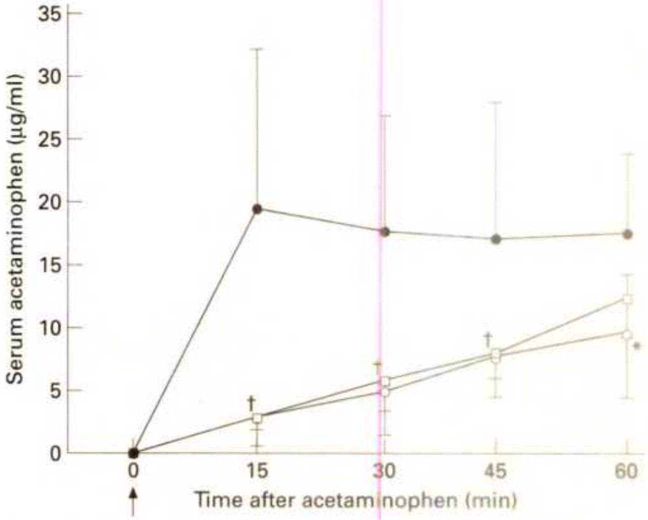

Fig. 3 Gastric emptying test by acetaminophen method before operation (□; $n = 6$), after distal gastrectomy (●; $n = 10$) and after pylorus-preserving gastrectomy (○; $n = 11$). Values are means (s.d.). $^*P < 0{\cdot}05$, $^\dagger P < 0{\cdot}01$ *versus* distal gastrectomy (unpaired Student's t test)

Gastric emptying test

The gastric emptying pattern of patients who had DG was rapid, following the so-called dumping pattern. However, the gastric emptying time of those who had a pylorus-preserving operation was significantly different, and was as slow as the normal preoperative pattern (*Fig. 3*).

Gallbladder contraction test

The gallbladder emptying of patients who had DG, which was disturbed markedly at 1 month after operation (data not shown), recovered well at 1 year after operation, but

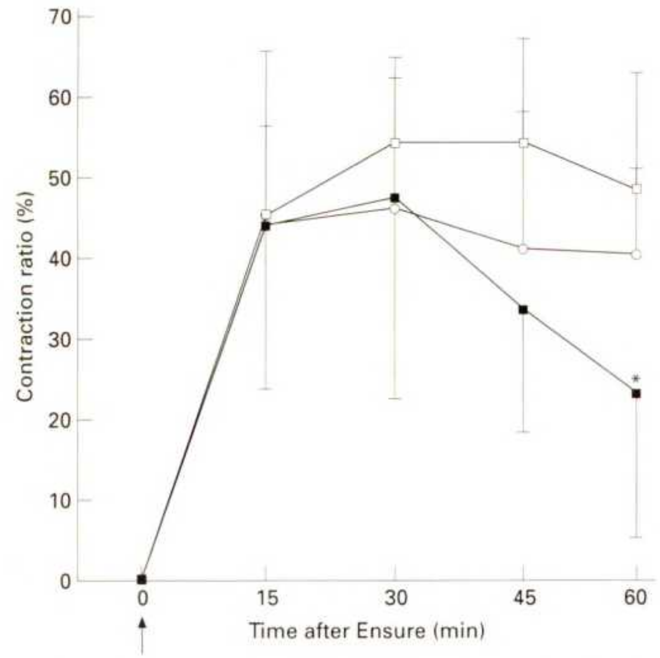

Fig. 4 Gallbladder emptying after the meal before operation (□; $n = 6$), after distal gastrectomy (■; $n = 10$) and after pylorus-preserving gastrectomy (○; $n = 6$). Values are mean (s.d.). $^*P < 0{\cdot}05$ *versus* pylorus-preserving gastrectomy (unpaired Student's *t* test)

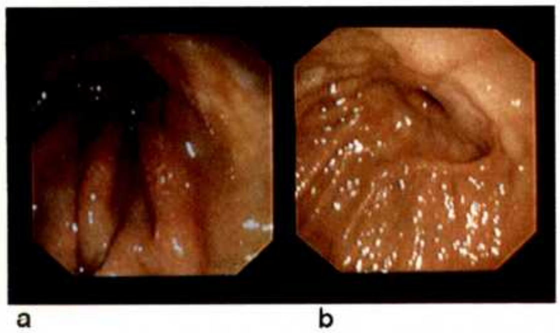

Fig. 5 Gastroscopy **a** after distal gastrectomy (DG) and **b** after pylorus-preserving gastrectomy (PPG). The mucosa of the stomach remnant after PPG was normal, while severe redness and oedema on the mucosa and regurgitation of duodenal juice were observed after DG

Table 1 Gastroscopic findings in the stomach remnant

	Findings in the gastric mucosa			Mean (s.d.) endoscopic gastritis score
	Redness	Oedema	Erosion	
PPG group ($n = 12$)	2	2	1	0·42(0·67)*
DG group ($n = 10$)	9	3	0	1·20(0·42)

PPG, pylorus-preserving gastrectomy; DG, distal gastrectomy. $^*P = 0{\cdot}004$ *versus* DG group, unpaired Student's *t* test

still had a tendency towards early re-expansion. In contrast, the gallbladder contraction of those who underwent PPG continued similarly to the preoperative pattern. A significant difference in the emptying ratio at 60 min after meals was detected between the PPG and the DG group (*Fig. 4*). No patient in the PPG group developed cholecystolithiasis after operation compared with one in the DG group.

Gastroscopy

Mucosal redness was observed in nine of ten patients who had DG, but in only two of 12 who underwent PPG. The mean endoscopic gastritis score in the PPG group (0·42) was significantly lower than that in the DG group (1·20, $P = 0{\cdot}004$), indicating a lower degree of gastritis in those who had PPG (*Table 1*). *Fig. 5* shows gastroscopic findings in typical patients of both groups. The mucosa of the remnant stomach after PPG was clear, while severe redness and oedema on the mucosa and regurgitation of duodenal juice was observed after DG.

Discussion

PPG in the treatment of gastric ulcer was clinically applied by Maki *et al.*[4], and satisfactory long-term results, including low incidence of dumping syndrome and ulcer recurrence, were reported. Although Maki and colleagues did not mention preservation of the vagus nerve, the present authors regard PPG for early gastric cancer as a function-preserving operation for this nerve. The present study demonstrated that PPG, in addition to preventing dumping syndrome[4,10], resulted in better maintenance of body-weight, gastric emptying pattern and contractility of the gallbladder than conventional DG with D_2 lymph node dissection. In other words, PPG produced satisfactory results as a function-preserving operation.

Cholecystolithiasis developed in 23·3 per cent of the patients who underwent distal gastrectomy with radical lymph node dissection in this institute[11], and disturbed the postoperative quality of life. The results of the gallbladder contraction test in the present study demonstrated that PPG with preservation of the vagus nerve might prevent cholelithiasis after operation. The greater ability of the gallbladder to contract may result from preservation of the nerve. However, the fact that the serum cholestokinin level after meals in the PPG group was similar to that in a normal group[11], probably resulting from the slower gastric emptying due to preservation of the pylorus, may play an important role in maintaining function of the gallbladder.

The indications for PPG are not the subject of the present study. However, this topic is important clinically. Kodama and Koyama[12] reported that the indications for PPG in patients with early gastric cancer located in the middle third of the stomach were any lesion smaller than 2·0 cm in maximum length, or a 2·0–4·0-cm lesion if it was a mucosal cancer. Based on studies of lymph node metastasis of patients with early gastric cancer in this institute (data not shown), the authors now adopt the following indications for PPG with preservation of vagus nerve: (1) Preoperative diagnosis of mucosal cancer; (2) For a lesion located in the distal third of the stomach, the maximum dimension of the lesion should be less than 20 mm for the elevated type in gross appearance, and less than 10 mm for the elevated and depressed type or the depressed type; (3) For a lesion located in the middle third of the stomach, the maximum dimension of the lesion should be less than 40 mm for the elevated type, and less than 20 mm for the elevated and depressed type or the depressed type[13]. Consequently, patients who had PPG in this series had mucosal cancers without histological evidence of lymph node metastasis.

The role of the pyloric branch of the vagus nerve in PPG is not clearly understood. In some institutes, PPG with complete D_2 lymph node dissection has been performed, and dissection of the suprapyloric lymph nodes with resection of the pyloric branch undertaken[14]. The indications for such a pylorus-preserving procedure with D_2 dissection could be wider than those for gastrectomy with preservation of the vagus nerve. It has been reported that the postoperative status after PPG without preservation of the vagus nerve is also better than that after conventional distal subtotal gastrectomy[15]. Comparison of the postoperative status after PPG with and without the preservation of vagus nerve should be performed in the future.

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Surgical workshop

Conversion operation for alkaline reflux after total gastrectomy and Schloffer reconstruction

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One of the most embarrassing symptoms after total gastrectomy and a serious cause of postoperative malnutrition is alkaline reflux. End-to-side oesophagojejunostomy with a jejunal loop and jejunojejunostomy is still used for gastric substitution and may be followed by alkaline reflux in up to 50 per cent of cases. Lawrence[1] first described a conversion operation in this situation with good clinical result but no other observations followed. In a series of four patients with alkaline reflux after this type of reconstruction a conversion operation based on the technical and functional experiences of the past decade[2–5] was used.

Surgical technique

In the years 1990–1994 four patients were admitted for treatment of severe entero-oesophageal alkaline reflux as a leading symptom after total gastrectomy. Two of them also showed signs of dumping. All patients had radical resection of gastric adenocarcinoma 4–7 years previously and no evidence of tumour recurrence. Reflux was proved by endoscopy with biopsy, conventional radiology and hepatoiminodiacetic acid-scanning. All patients were suffering from severe malnutrition and disabling symptoms (Visick grade 3–4). After operation all patients were followed up by reinvestigation every 3 months in the first year and then at half-yearly intervals. The postoperative weight gain was calculated as a percentage of preoperative weight.

The abdomen was explored through an upper midline incision to exclude the presence of tumour. Then the enteroanastomosis was cut with a linear stapler (GIA 90, AutoSuture, Ascot, UK) and the ascending loop was transected 7 cm below the oesophagojejunostomy (*Fig. 1*). The blind loop below the anastomosis was closed with a stapler (TA 55, AutoSuture), and used as a ventral hemijejunoplication to prevent reflux. The procedure was finished by a Roux-en-Y reconstruction with a proximal limb at least 50 cm in length.

Results

The operating time was 95–135 min. Only one patient needed 2 units of blood. No major complications occurred. The length of hospital stay was 12–17 days. All patients reported complete resolution of reflux symptoms immediately after the operation. In the follow-up period weight gain (10–27 per cent) was observed in all cases. The actual Visick grading of three patients under long-term observation (11–51 months) was 1, 2 and 2. One patient with persisting dumping symptoms improved only from grade 4 to 3 after 5 months.

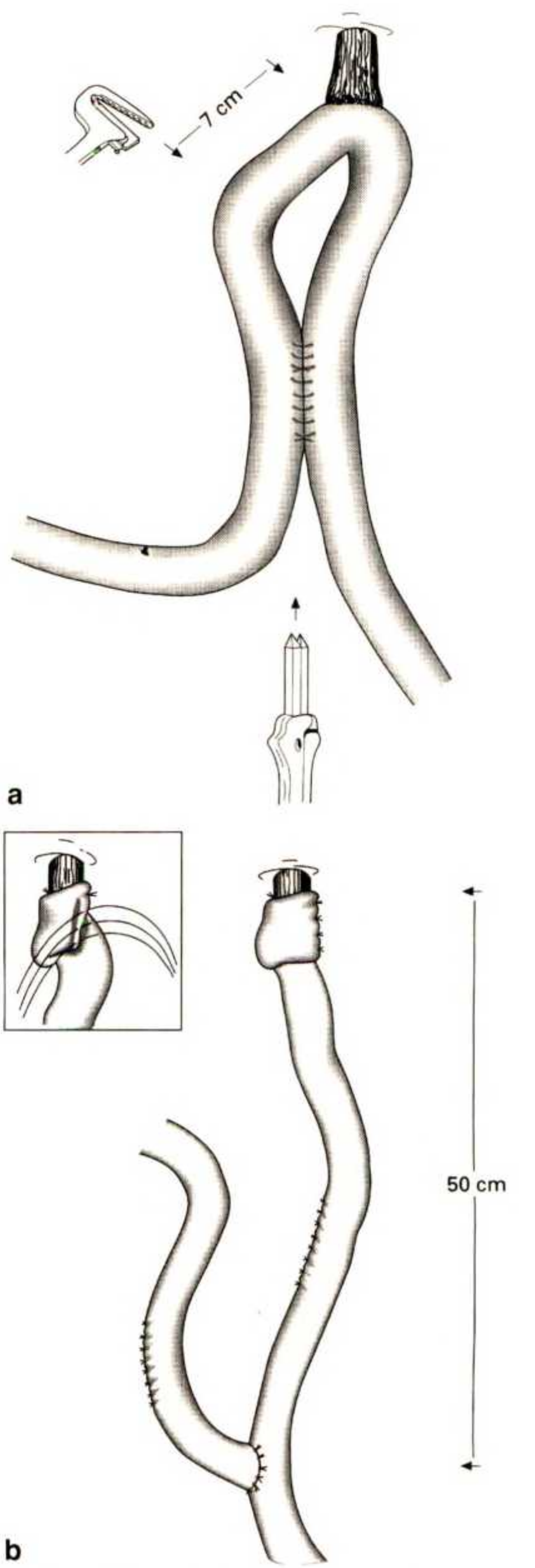

Fig. 1 **a** Anatomical situation of a jejunal loop with jejunojejunostomy showing sites of transection. **b** Completed conversion to a Roux-en-Y reconstruction with ventral hemijejunoplication

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Discussion

Alkaline reflux after total gastrectomy and end-to-side anastomosis with lateral jejunal anastomosis is common and can be treated effectively by conversion into a Roux-en-Y arrangement. The main factor preventing reflux is a long Roux loop of at least 50 cm[2,5]. Additionally, a ventral hemijejunoplication helps to prevent reflux. A complete jejunoplication should not be used because it can lead to obstruction[3]. The technique presented here is easy and safe and might only have restrictions in the resolution of dumping symptoms[4]. The present results are excellent for the therapy of alkaline reflux and may give rise to wider use of the procedure.

Acknowledgements

Fig. 1 was drawn by M. Rau, Department of Surgery, RWTH Aachen.

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Short note

Intraoperative fine-needle aspiration cytology of abdominal lesions – a safe alternative to surgical biopsy

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As a diagnostic tool, intraoperative cytology offers simplicity, speed, accuracy, excellent cellular detail and thus several advantages over conventional frozen section techniques[1–3]. Unfortunately, it is not being used to its fullest extent. In a recent study[2], only 13 per cent of the surgeons who responded to a questionnaire used intraoperative cytology more than 5 per cent of the time. The authors' experience with intraoperative fine-needle aspiration cytology (FNAC) of abdominal lesions is presented.

Patients and methods

Forty-three patients, who underwent laparotomy during a 12-month period, constituted the study group. Cytological material was procured by fine-needle aspiration from *in situ* mass lesions during the operation. Two sets of smears stained with May–Grüenwald–Giemsa stain and Papanicolaou's stain were examined, and a cytological diagnosis was reached. Efforts were made to obtain tissue from each lesion for histopathological examination, which was conducted 'blind'.

Results

Fifty-six mass lesions were evaluated by intraoperative FNAC. Resected specimens or surgical biopsies of 43 lesions were available for histopathological examination. Surgical biopsy of 13 irresectable lesions was avoided by the surgeon for reasons shown in *Table 1*. No complication of intraoperative FNAC was observed. Duodenal wall perforation occurred while performing wedge biopsy in one patient.

The cytological diagnosis agreed with the histological diagnosis for 40 of 43 lesions. There was discrepancy regarding the type of malignancy in respect of a case of pancreatic lymphoma which was diagnosed as adenocarcinoma cytologically. Intraoperative cytological analysis was non-diagnostic for two lesions, namely adenocarcinoma of the gallbladder and retroperitoneal lymphangioma. FNAC revealed malignancy in 24 of 25 malignant lesions. It was possible to identify tuberculous pathology in cytological smears from all ten tuberculous lesions. Intraoperative FNAC was successful in providing microscopic diagnosis in 12 of the 13 lesions in which the surgical biopsy was not considered safe or feasible (*Table 1*).

Discussion

The surgeon often needs microscopic confirmation of the clinical diagnosis before undertaking major resection[4]. In addition, microscopic diagnosis is required for planning subsequent management of irresectable lesions. Although intraoperative FNAC can be performed on any mass lesion, the same is not true for surgical biopsy. Limitations and complications of wedge biopsy are well documented in the literature[3,5,6]. During the present study wedge biopsy of a duodenal mass resulted in perforation of the viscus. Because of the risk of complications, the surgeon often refrains from performing peroperative surgical biopsy. In various series evaluating intraoperative cytology, concomitant surgical biopsy for the same site was available in 28–83 per cent of cases[2–6]. It was considered unsafe to perform surgical biopsy in 13 of the 56 lesions (23 per cent) in this study. Intraoperative FNAC could be performed safely in each of these lesions, resulting in microscopic diagnosis in 12 cases (*Table 1*). Intraoperative FNAC permits more accurate sampling from deeply seated lesions[3]. No complication has been reported following this procedure on *in situ* pancreatic[3–5], colonic[6] or bile duct lesions[7].

The availability of well trained cytotechnologists and cytopathologists is mandatory for accurate cytological analysis. The frequency of non-diagnostic results can be reduced by updating the surgical team on proper techniques for obtaining and preparing specimens for

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Table 1 Reasons for avoiding surgical biopsy of 13 lesions

Site	Reasons for avoiding biopsy	Diagnosis*
Duodenum	Risk of viscus perforation	Adenocarcinoma
Pyloric region	Risk of viscus perforation	Granulation
Caecum	Risk of viscus perforation	Adenocarcinoma
Gallbladder (3 lesions)	Risk of viscus perforation	Adenocarcinoma
Bile duct	Inaccessibility, distorted anatomy and risk of duct perforation	Cholangiocarcinoma
Lymph node	Close proximity and adherence to blood vessel; risk of haemorrhage	Inadequate material
Lymph node (2 lesions)	Close proximity and adherence to blood vessel; risk of haemorrhage	Adenocarcinoma
Pancreas	Risk of pancreatic duct perforation and haemorrhage	Granulation
Pancreas	Risk of pancreatic duct perforation and haemorrhage	Adenocarcinoma
Rectovaginal septum	Inaccessibility and risk of rectal perforation	Granulation

*By intraoperative fine-needle aspiration cytology

cytology[2]. With the use of rapid staining methods, the procedure can be completed in less than 5 min[1,3]. The cytology report may be delivered to the surgeon expeditiously, as early as[6] or even before[2] the frozen section diagnosis, and inconclusive reports may be followed by repeated aspirations[5].

In the authors' experience, intraoperative FNAC is a simple, accurate and safe technique. It permits microscopic evaluation of lesions that are not suitable for surgical biopsy and can be used as an alternative to surgical biopsy in selected cases.

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Conservative treatment *versus* antireflux surgery in Barrett's oesophagus: long-term results of a prospective study

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The results obtained for the treatment of 59 patients diagnosed with Barrett's oesophagus, randomized to receive medical treatment ($n = 27$) or antireflux surgery ($n = 32$) were assessed prospectively. Median follow-up for the patients undergoing medical treatment was 4 (range 1–11) years and for patients undergoing surgical treatment 5 (range 1–11) years. Satisfactory symptomatic control (excellent to good results) was achieved in 24 patients after medical therapy and in 29 after antireflux surgery. The proportion of patients with persistent inflammatory lesions (54 per cent) and persistent or recurrent stenosis (47 per cent) was significantly higher after conservative treatment than after surgery (5 and 15 per cent, respectively). A decrease in the length of the segment of columnar mucosa was observed in eight of the patients who underwent antireflux surgery, and in only two of those given medical therapy. Conversely, an upward progression of the columnar lining was more frequent in the latter group (11 *versus* three). Mild dysplasia was observed in five patients, all from the group undergoing medical treatment. Severe dysplasia was detected in two patients, one undergoing medical treatment and the other following surgical therapy, in whom an antireflux procedure had failed previously. Both patients underwent oesophageal resection, with confirmation of a carcinoma *in situ*. The patients in whom antireflux surgery proved effective showed no dysplastic change or progression to adenocarcinoma. These results, despite the small number of patients and methodological limitations, question the systematic conservative approach in the initial management of patients with Barrett's oesophagus.

Treatment for Barrett's oesophagus is controversial. Conservative therapy with antisecretory drugs should be maintained for life[1], even if the patient is asymptomatic, as it does not cause the metaplasia to disappear[2,3], and cannot restore a normal lower oesophageal sphincter (LOS) and effective oesophageal clearing function[4,5]. Furthermore, it does not control the biliopancreatic component of the reflux involved, in clinical[6,7] and experimental studies[8], in the development of complications in addition to Barrett's oesophagus. On the other hand, antireflux surgery, which has proved effective in preventing reflux in 80–90 per cent of patients with long-term follow-up[9–11], does not lead to the disappearance of Barrett's oesophagus either, as has been reported by most authors[12–16], with progression to adenocarcinoma in some cases[16,17]. It can even produce side-effects and is not exempt from morbidity or mortality[11,18,19].

In this context, it would be interesting to compare the two types of treatment in a long-term prospective study, evaluating the progression or regression of the metaplastic segment, changes in the type of epithelium, percentage of patients in whom dysplasia appeared or developed from mild to severe, and the evolution of strictures and/or ulcers and other inflammatory phenomena.

This paper aims to present a long-term prospective study and to compare the results of conservative treatment and antireflux surgery in patients with Barrett's oesophagus.

Patients and methods

Between January 1982 and January 1993 a total of 90 patients diagnosed with Barrett's oesophagus were studied. The condition was considered when endoscopy demonstrated a circumferential segment of columnar epithelium over 3 cm in length and continuing into the cardia, confirmed histologically.

Excluded from the study were 21 patients with stenosis of more than 1 cm in length and/or less than 1·2 cm in diameter. Also excluded were 10 patients who rejected annual follow-up endoscopy. The study, therefore, considers 59 patients. Randomization was performed using a random number sequence before assessment. Two groups of patients were formed (medical treatment, $n = 27$; antireflux surgery, $n = 32$), which were homogeneous with regard to epidemiological, clinical, endoscopic, histological, manometric and pH-metric data (*Tables 1* and *2*).

Medical treatment for all patients ($n = 27$) consisted of hygiene, diet and postural measures associated with antisecretory drugs (H_2 antagonists initially and omeprazole from 1992 onwards for all), and periodical dilatations in patients with stenosis. Median follow-up was 4 (range 1–11) years.

Surgical treatment in 30 patients consisted of a short Nissen fundoplication (1·5–2 cm) over a 48–50-Fr bougie and in the remaining two, when oesophageal shortening prevented the achievement of a sufficient length of intra-abdominal oesophagus, a Collis–Nissen procedure was performed. The abdominal route was used in all patients. Dilatations were carried out before and after operation in patients with stenosis. Median follow-up was 5 (range 1–11) years.

All patients underwent annual clinical, endoscopic and histological assessment. To check the efficiency of the antireflux procedure, operated patients received pH-metric and manometric controls 1 and 5 years after surgery.

Clinical assessment was made by personal interview, always by two surgeons, and the results were classified as excellent (asymptomatic), good (with minimal symptoms requiring no therapy), fair (improved but with symptoms requiring intermittent therapy, e.g. dilatation or antireflux medication in cases of surgery), and poor (unimproved or worse).

Endoscopic assessment was made in all patients by the same endoscopist. To measure the length of segment of Barrett's oesophagus, the incisors, squamo–columnar junction and cardia were taken as reference points. Progression or partial regression of Barrett's oesophagus was considered when the length of the

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Barrett's segment increased or decreased at least 1 cm compared with the pretreatment length. Multiple biopsies were taken systematically during endoscopy: the first immediately above the squamo–columnar junction, the next immediately below, and the rest every 1–2 cm in a caudal direction in the various quadrants of the circumference. Dysplasia was graded according to Riddell *et al.*[20]. Following these criteria, low-grade dysplasia was characterized by glands lined by cells with enlarged hyperchromatic nuclei and nuclear crowding with stratification. High-grade dysplasia was characterized by nuclear stratification extending to the luminal surface of glands, marked nuclear pleomorphism or loss of nuclear polarity. When acute inflammation was present, the cytological changes were graded as indefinite for dysplasia.

Manometry and pH studies were performed before therapy was started, and to check the efficiency of the antireflux procedure, the operated patients received pH-metric and manometric controls 1 and 5 years after surgery. The manometric study was performed using a probe with three microtransducers (Gaeltec Pressure Microtransducers, Dunvegan, UK) located at the distal end 120 radially to one another and spaced 5 cm apart, and a Hewlett-Packard 7754 B System polygraph (Palo Alto, California, USA). The method used to perform the oesophageal intraluminal manometry has been described previously[21]. Midrespiratory LOS pressure relative to the gastric baseline was measured by the slow pull-through technique. Total length was calculated as the length of the sphincter between the initial rise above the gastric baseline and the return of the tracing to the oesophageal baseline. Intra-abdominal length was calculated as the length of the sphincter between the initial rise above the gastric baseline and the respiratory inversion point. The LOS pressure (expressed in mmHg), as well as the value of its total and intra-abdominal length (given in centimetres), represent a mean of values from the three lumina of the catheter. The points chosen to measure oesophageal peristalsis were located at 2, 7 and 12 cm above the LOS and the patient was instructed to make ten swallows of a 5-ml water bolus. The following parameters were studied in the distal third of the oesophageal body: mean amplitude of the contractile waves (expressed in mmHg), mean percentage of simultaneous waves over a 5-cm segment (the waves were considered simultaneous when they began at the same time at two or three adjacent recording sites), and mean percentage of interrupted waves (waves that failed to traverse the entire length of the oesophagus).

Table 1 Age, sex, clinical, endoscopic and histological data of patients

	Group I ($n = 27$) Conservative treatment	Group II ($n = 32$) Surgical treatment
Age (years) (median (range))	40 (12–78)	32 (10–71)
Sex (M:F)	20:7	20:12
Duration of symptoms (years) (median (range))	19 (2–50)	15 (1–50)
Symptoms		
Heartburn	24 (89)	29 (91)
Regurgitation	20 (74)	24 (75)
Dysphagia	14 (52)	16 (50)
Haemorrhage	6 (22)	10 (31)
Endoscopic data		
Oesophagitis	13 (48)	22 (69)
Barrett's ulcer	4 (15)	4 (12)
Stricture	17 (63)	13 (41)
Length of Barrett's segment (cm) (median (range))	4 (3–12)	5 (3–14)
Types of epithelium		
Specialized	7 (26)	7 (22)
Junctional	4 (15)	4 (12)
Fundic	0	0
Two or more types	16 (59)	21 (66)
Dysplasia	0	0

Values in parentheses are percentages except where stated

Twenty-four-hour pH monitoring was performed in all patients with a Synectics (Synectics, Stockholm, Sweden) portable pH measuring unit The equipment consisted of a monocrystal-line antimony pH electrode, a silver–silver chloride reference electrode and a solid state box. After calibration at pH 7 and 1, the pH electrode was passed through the nose and positioned in the oesophagus 5 cm above the LOS, previously located by manometry. The reference electrode was placed on the chest and the memory box was worn in a waistbelt. The patients were instructed to lead as normal a life as possible and to take normal meals with the exception of acid food and beverages Medication against gastro-oesophageal reflux was withdrawn before the study (48 h for H_2 antagonists and 7 days for omeprazole). After the monitoring period, the data were analysed by a computer program (Esophogram Gastrosoft, Irving, Texas, USA) on an IBM personal computer. Following the methodology of Johnson and De Meester[22], the cumulative exposure of the oesophagus to acid was expressed as the percentage of time for which the pH was less than 4 during the study period, and defined as abnormal when it exceeded 4·5 per cent.

The mean, standard deviation, median and range were calculated for all data. The Wilcoxon rank sum test for paired or unpaired data, depending on the groups compared, was used for comparative studies. For comparison of non-quantitative variables the χ^2 test was used

Results

The clinical results in patients undergoing medical treatment were excellent for 15 patients, good for nine and fair for the remaining three. Three patients required dilatation with a median of three (range 2–7) dilatations. There were no deaths after surgical treatment; one

Table 2 Manometric and pH-metric data before treatment

	Group I ($n = 27$) Conservative treatment	Group II ($n = 32$) Surgical treatment
Manometric data		
Total length of LOS (cm)	2 (1–4·5)	2 (1·5–4)
Abdominal length of LOS (cm)	0 (0–1·7)	0·5 (0–2)
Resting pressure of LOS (mmHg)	6·2 (0–16)	8·2 (0–19)
Amplitude of contractile waves (mmHg)	27 (0–101)	35 (9·5–147)
Percentage of simultaneous waves	6 (0–100)	0 (0–100)
Percentage of interrupted waves	0 (0–100)	0 (0–72)
pH-metric data		
Percentage of time with pH < 4	17 (1–76)	17·2 (3–83)

Values are median (range). LOS, lower oesophageal sphincter splenectomy was performed as a result of an irreparable splenic capsular laceration, and nine patients showed difficulty in belching and vomiting, which was mild and transitory in all patients. The results were considered excellent in 25 patients, good in four and fair in the remaining three, with no significant differences between the groups. Postoperative dilatation was necessary in one patient who required two dilatations (not significantly different from conservative treatment).

The endoscopic and histological appearances before and after treatment are shown in *Table 3*. The Barrett's ulcers were cured with both types of treatment. However, surgical treatment proved more efficient than medical therapy in curing oesophagitis (95 *versus* 46 per cent; $P<0\cdot05$), in curing the stenosis (85 *versus* 53 per cent; $P<0\cdot05$) and in stabilizing the length of the metaplastic segment. As can be seen in *Fig. 1*, the length of the Barrett's segment in the medical treatment group decreased in two patients, increased in 11 and remained unchanged in the remaining 14. After antireflux surgery (*Fig. 2*) the length of the Barrett's segment decreased in eight patients, increased in three and remained unchanged in 21. The distributions in the two groups were significantly different ($\chi^2=9\cdot21$; 2 d.f.; $P<0\cdot01$). In the patients with a decreased metaplastic segment, the biopsies taken immediately above the squamo–columnar junction confirmed the existence of squamous epithelium. Dysplasia appeared in six patients undergoing medical treatment (mild in five and severe in one), whereas it occurred in only one patient who had surgery (which was severe). The two patients with severe dysplasia underwent oesophageal resection, and the presence of carcinoma *in situ* was confirmed. The rate of malignancy was one in 127 patient/years for the medical treatment group and one in 160 patient/years for the surgical treatment group, with no significant differences; however, it must be noted that the pH-metric monitoring performed in the operated patient, 1 year after surgery, revealed failure of the antireflux procedure, with a percentage of time with pH less than 4 of 37 per cent.

Table 4 shows that antireflux surgery improves the mechanical condition of the LOS and the quality of oesophageal peristalsis. The median percentage of time with pH less than 4 in the postoperative controls was 1 per cent, although it must be noted that five of 32 patients demonstrated pathological rates of reflux (median 12 per cent, range 5–37 per cent).

Table 3 Endoscopic and histological findings before and after treatment

	Medical		Surgery	
	Before treatment	After treatment	Before treatment	After treatment
Endoscopic data				
Oesophagitis	13	7	22	1
Barrett's ulcer	4	0	4	0
Stricture	17	8	13	2
Length of Barrett's segment (cm) (median (range))	4 (3–12)	5 (3–12)*	5 (3–14)	4·5 (3–13)
Histological data				
Mild dysplasia	0	5	0	0
Severe dysplasia	0	1	0	1†

*$P<0\cdot01$; †for this patient the percentage of time with pH less than 4 was 37 per cent 1 year after surgery

Discussion

Treatment of Barrett's oesophagus is controversial. Most authors treat it as they do any patient with gastro-oesophageal reflux disease (GORD), beginning with conservative therapy and reserving antireflux surgery for failure to control symptoms[16,23]. The fundamental difference between this therapeutic approach and that used for oesophagitis without Barrett's oesophagus lies in the need for periodic endoscopic controls to detect the possible appearance of dysplasia and/or carcinoma. However, this

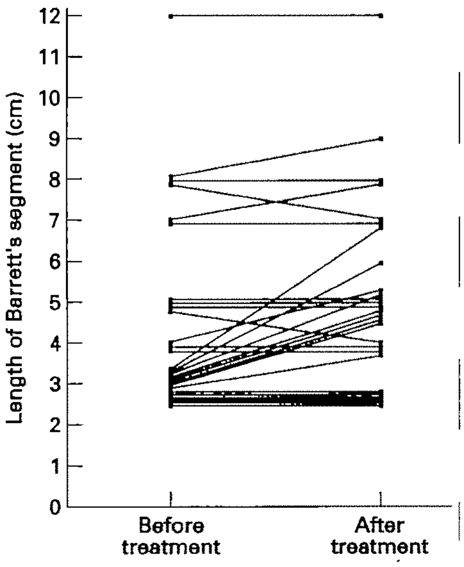

Fig. 1 Length of Barrett's segment before and after medical treatment

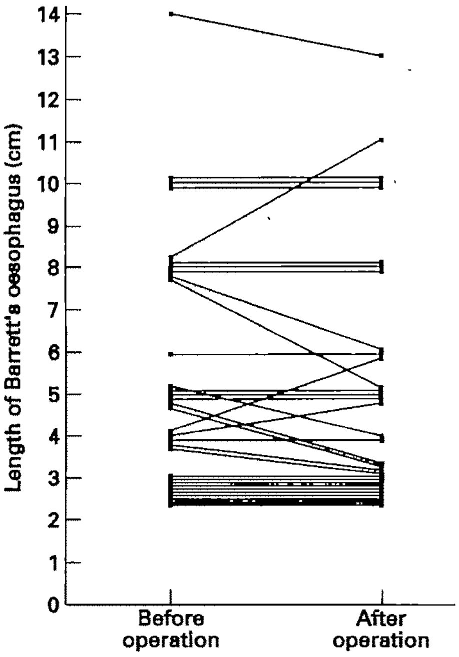

Fig. 2 Length of Barrett's segment before and after surgical treatment

Table 4 Manometric and pH-metric data before and after antireflux surgery ($n = 32$)

	Preoperative	Postoperative
Manometric data		
Total length of LOS (cm)	2 (1·5–4)	3·5 (2·5–5)*
Abdominal length of LOS (cm)	0·5 (0–2)	3 (0–3·8)*
Resting pressure of LOS (mmHg)	8·2 (0–19)	16·5 (5·5–29)*
Amplitude of contractile waves (mmHg)	35 (9·5–147)	42 (20–136)*
Percentage of simultaneous waves	0 (0–100)	0 (0–75)
Percentage of interrupted waves	0 (0–72)	0 (0–66)†
pH-metric data		
Percentage of time with pH<4	17·2 (3–83)	1 (0–37)‡

Values are median (range). LOS, lower oesophageal sphincter. $^{*}P<0{\cdot}01$; $^{\dagger}P<0{\cdot}05$; $^{\ddagger}P<0{\cdot}001$

opinion is questionable, as the treatment should be maintained for life[1]. Patients occasionally require large doses of antisecretory drugs to control the symptoms and cure the endoscopic lesions, which is expensive and may lead to the appearance of side-effects related to hypergastrinaemia[24]. Furthermore, this treatment does not modify the defective mechanical condition of the LOS and the impaired motor activity of the oesophagus, which means it does not prevent the alkaline reflux and further tissue destruction involved in the appearance of complications in addition to Barrett's oesophagus[4,5].

Considering the obvious premalignant potential of Barrett's oesophagus, an alternative could be to replace conservative treatment by antireflux surgery, especially in young patients. Conservative treatment would only be indicated in patients who were elderly or had organic disease that increased the risk of surgery. Surgery prevents the possibility of reflux, acid or alkaline, by improving the mechanical conditions of the LOS, although complete regression of metaplasia is exceptional[12–16]. Therefore, although patients need no medication, they should be monitored as though following conservative treatment.

To date, the choice of either therapeutic approach is based more on personal criteria than on objective data from comparative prospective studies; the initial conservative attitude is predominant[16,23]. Only Spechler[25] found that antireflux surgery was significantly more effective than conventional medical therapy (without omeprazole) in improving the symptoms and endoscopic signs of oesophagitis for up to 2 years in patients with complicated GORD.

In the authors' experience, conservative and surgical treatment proved equally effective in controlling symptoms. However, the same was not true when evaluating associated endoscopic lesions, as the percentage of patients with oesophagitis and persistent stenosis was significantly higher in the patients undergoing medical treatment (seven and eight respectively) than in those receiving antireflux surgery (one and two). Regression of the metaplasia is difficult to assess as it can occur circumferentially or leaving islands or metaplastic tongues among normal epithelium. The presence of regenerating squamous epithelium overlying residual columnar mucosa has also been reported[26], for which reason biopsies of insufficient depth may not detect residual columnar epithelium. Furthermore, after antireflux surgery the distance between the incisors and squamo-columnar junction may be modified by the surgical manoeuvres, which means the cardia must also be taken as a reference point. All these methodological problems explain why there are no conclusive data on the regression of Barrett's oesophagus, although it has been reported occasionally, more frequently after antireflux surgery[26,27]. Total regression of the metaplastic segment was not observed in any patient although, as can be seen in *Figs 1* and *2*, partial regression was noted in eight of the patients undergoing antireflux surgery and in only two of the patients treated conservatively. Conversely, extension of the Barrett's oesophagus was more frequent after conservative treatment.

The appearance of dysplastic changes in addition to Barrett's oesophagus, and especially their disappearance after treatment, must be assessed with caution. The patchy nature of the lesion may lead to sampling error that can lead to false-negative biopsies, for which reason any study to assess dysplasia must include multiple biopsies along the whole of the metaplastic segment and in different sectors of the circumference. In the present study, dysplastic changes appeared in seven patients (two severe dysplasias), six undergoing medical treatment and one following antireflux surgery. The latter received a Nissen procedure in 1983 for Barrett's oesophagus with inflammatory lesions. One year after surgery, clinical evaluation was fair and 24-h pH monitoring showed 37 per cent of time with pH less than 4, for which reason the patient was treated with H_2 antagonists and given an annual endoscopic control. In 1990, high-grade dysplasia was detected and an oesophageal resection performed.

If the five patients in whom antireflux surgery failed are combined with the medical treatment group ($n = 32$) and compared with the 27 patients with successful antireflux surgery, it can be seen that dysplastic changes appeared in seven of the former and none of the latter, with statistically significant differences. Patients who had conservative treatment or failed surgery showed an increased rate of malignancy (one of 82 patient/years), whereas the patients who underwent antireflux surgery had a zero rate.

In conclusion, although the clinical results are similar with both types of treatment, the endoscopic and histological modifications in this series, despite the small number of patients and methodological limitations, question the advantages of the systematic conservative approach in the initial management of patients with Barrett's oesophagus. In the authors' opinion antireflux surgery should be offered to young people especially because a lifetime of medication will be necessary and the results of medical therapy are inferior to antireflux surgery. Further prospective studies are necessary to elucidate this question.

Acknowledgements

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British Journal of Surgery 1996, 83, 279–283

Correspondence

Healing process of sutureless choledochojejejunostomy in an experimental model

Sir

I read the article by Dr Ishizaki and colleagues (*Br J Surg* 1995; 82: 1118–21) with great interest. Their results indicate that the sutureless anastomosis in a rat experimental model is reliable and leads to long-term anastomotic patency 52 weeks after surgery.

Three years ago I operated on an obese 71-year-old woman on long-term steroid treatment who had developed perforation of the gallbladder with biliary peritonitis. The common hepatic duct was injured and reoperation was required. The proximal bile duct was cannulated externally, and the distal duct ligated. Despite daily peritoneal lavage a necrotic process spread proximally along the cannulated common hepatic duct, so subsequently both hepatic ducts were stented. Each tube was tied into the duct and its distal end was inserted into a 45-cm Roux-en-Y jejunal loop and held in place by a purse-string suture. After a transient external biliary fistula the patient recovered, and she remains alive and well.

The decision for this sutureless hepaticojejunostomy was based on previous experience of ten stented biliodigestive anastomoses for unresectable carcinoma involving the hepatic hilus[1].

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Randomized trial of laparoscopic cholecystectomy and mini-cholecystectomy

Letter 1

Sir

Mr McGinn and colleagues (*Br J Surg* 1995; 82: 1374–7) have failed to demonstrate clear-cut differences in early outcome between laparoscopic and 'minilap' cholecystectomy in a controlled trial undertaken in circumstances that more closely resemble the real world than do many reports extolling the allegedly unassailable benefits of the laparoscopic procedure.

Surgeons in the Burnie Hospital have long been so satisfied with the minilap operation that we have felt unable to subject ourselves, our trainees and, more importantly, our patients to the risks of the learning curve that have been the sad, but usually unpublished experiences of many otherwise safe and competent surgeons. Anyone drinking coffee at a surgical meeting anywhere in the world hears too many horror stories for these to be dismissable simply because they are anecdotal.

We find that a short high transverse right upper quadrant incision, commencing almost on the midline and retracting the rectus muscle laterally, gives an even less painful wound than a short muscle-cutting incision. Whether they be public or private, more than half our patients spend two nights in hospital or less[1]. This series included all comers, including junior trainees operating under supervision. Private patients are still coming for the minilap procedure, despite the availability of the laparoscopic operation not far away.

Laparoscopic cholecystectomy has been described in this and other journals as the 'gold standard' more times than any of us can count. Those who do so ought to remember that the original gold standard was only introduced because a lot of gold had been discovered in the USA, and that it is more than 20 years since the last remaining monetary authority went off it. Thus there are sound semantic reasons why surgical writers should drop this tired cliche

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Editorial footnote

Without wishing to comment on the relative merits of the various techniques for removing the gallbladder, the Editors agree that the term 'gold standard' is becoming an overworn cliche. Perhaps a new term is required to describe techniques that have become established as a yardstick (another cliche) and against which subsequent procedures can be compared

Letter 2

Sir

We would like to congratulate Mr McGinn and his colleagues (*Br J Surg* 1995; 82: 1374–7) for demonstrating again that there is very little difference in outcome between mini-cholecystectomy and laparoscopic cholecystectomy. However, there is a number of areas in the manuscript that concern us. We find it difficult to understand how a conversion rate of 13 per cent will increase the median hospital stay of the laparoscopic group from 2 to 4 days Were patients converted to mini-cholecystectomy, which had a median hospital stay of 3 days, or to conventional cholecystectomy and, if conventional, why?

This study demonstrates a 4½-week difference between groups for return to normal activity in favour of laparoscopic cholecystectomy. This finding is inconsistent with results from other randomized clinical trials[1,2], which show a much more modest advantage for laparoscopic cholecystectomy (7–10 days). How was return to normal activity assessed? Specifically what postoperative activities were assessed and who made the assessment?

We disagree with the suggestion that a conversion rate of 10–15 per cent is necessary if serious complications are to be avoided with laparoscopic cholecystectomy. Since we completed a multicentre trial comparing minilaparotomy and laparoscopic cholecystectomy in April 1993[1], our unit has continued to gather data on laparoscopic cholecystectomy prospectively. Like McGinn *et al.* we have not had a bile duct injury in our laparoscopic series. When we compare the 50 laparoscopic and 50 minilaparotomy cholecystectomy patients entered into the multicentre trial[1] from our unit with our last 50 laparoscopic cholecystectomies, we see that as surgeons become more experienced with the technique, conversion rates decrease without a change in complication rates. Furthermore, operating time significantly decreases ($P = 0{\cdot}0084$) and becomes similar to that of mini-cholecystectomy (*Table 1*).

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Table 1 Comparison of laparoscopic and mini-cholecystectomy

	Operating time (min)	Conversion rates	Complications
Mini-cholecystectomy 1992/1993	45 (40–55)*	8%	4%
Laparoscopic cholecystectomy 1992/1993	65 (46–70)*	8%	4%†
Laparoscopic cholecystectomy 1995	50 (40–66)*	2%	4%‡

*Values are median (interquartile range). †Two bile leaks; ‡one postoperative myocardial infarction, one subcutaneous abscess secondary to stone spillage

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Authors' reply

Sir

Thank you for giving us a chance to reply to the letter from Messrs Wallace, McMahon and O'Dwyer. The majority of the laparoscopic patients who needed to be converted were, in fact, converted to conventional cholecystectomy. The reason for this is that the majority of conversions involved senior registrars in training and we felt that it was safer for patients to be converted to a wider incision so that the problem which had arisen from the laparoscopic approach could be dealt with safely and accurately.

Return to normal activity was determined at follow-up and was really dictated by the patient's general practitioner (GP). There is no doubt, over the first few years of our trial, that patients and GPs were influenced by media stories that it was, indeed, possible to get back to work earlier after laparoscopic procedures; we would agree that the difference in return to normal activity is a very poor indicator of the success of any operation because it is such a subjective value.

We agree that our conversion rate seems high for laparoscopic cholecystectomy but point out that ours was not a multicentre trial in which it would be extremely difficult to standardize procedures and, inevitably, very different standards of surgery and surgeon are involved in multicentre trials. We have observed that the conversion rate of surgeons in training is much higher than that of consultant surgeons who have been familiar with each procedure for much longer. One of the problems with the Glasgow multicentre trial is that it would have been impossible to establish equal enthusiasm and experience of the surgeons involved, particularly with the performance of mini-laparotomy cholecystectomy. We reported a prospective trial to simulate what the conditions would be in the 'real world' when surgeons in training have been included in the trial once they have been given the opportunity to become adequately experienced in each procedure. We would also like to point out that our only exclusion from the trial was that of emergency cholecystectomy and that many patients who would otherwise have been excluded from laparoscopic procedures, such as those with infection, empyema, previous upper abdominal surgery etc, were, in fact, included in our trial so that we could be completely fair about the entry of patients with potentially the same problems.

We imagine that very few of Mr O'Dwyer's last 50 laparoscopic cholecystectomies were performed on patients who were admitted as emergencies and were then operated upon on the next list within 2 or 3 days of admission It is this sort of patient in whom we have the most problems with laparoscopic procedures.

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Postocclusive hyperaemic duplex scan: a new method of aortoiliac assessment

Sir

I read with interest the article by Mr Currie and colleagues (*Br J Surg* 1995; 82: 1226–9) and wholeheartedly agree that there is a need for a quick, easy, non-invasive method for determining the presence of aortoiliac disease in patients being considered for treatment. I would however like to raise a number of points.

(1) No evidence was presented to support the validity of inflating the thigh cuff to brachial pressure for 3 min to create a hyperaemia equivalent to that produced by an intra-arterial injection of papaverine 30 mg. While there is evidence that this dose of papaverine is sufficient to produce a maximum hyperaemia[1], previous reports do not agree on the optimum occlusion time for postocclusive hyperaemia[2–4]. Indeed there is evidence to suggest that occlusion combined with exercise until claudication appears is required reliably to achieve a maximum hyperaemia[4, 5] Also, as the normal thigh:brachial index is around 1·5[6], a thigh cuff should be inflated to a pressure at least 50 per cent greater than the brachial systolic pressure to achieve occlusion of the thigh vessels.

(2) I would question the value of presenting positive predictive values (PPVs) and negative predictive values (NPVs) in preselected groups. The sensitivity and specificity statistics are, in theory, independent of the prevalence of a given outcome, but PPV and NPV are not[7]. Given that the prior probability of each outcome is already known in the first group of patients (i.e. 50 per cent), the PPV and NPV can be calculated from the sensitivity and specificity, and so add nothing to the results.

(3) The assumption of a resting systolic pressure gradient of 20 mmHg as an indicator of important aortoiliac disease was suspiciously unqualified. In their extensive review of the subject, Baker *et al.*[8] were unable to give a reliable value, and there is evidence that significant disease may produce a resting gradient considerably less than this[9, 10]. Given that the pressure gradient is related to the flow and that there is a wide variation in resting flow between individuals[11], it is no surprise that the resting pressure gradient cannot reliably discriminate.

(4) The use of 'statistical trawling' to find the most discriminant thresholds suggests a basic lack of design and the absence of a testable hypothesis that relates the measured parameters with the severity and distribution of the arterial disease. Even if, given enough patients, a statistical difference can be shown for a particular parameter, any overlap of the diagnostic groups indicates that the parameter has a limited predictive value for individual patients. Indeed there is evidence that no single parameter can accurately determine both the severity and distribution of multisite disease[12], and so some form of multiparameter cluster analysis or modelling, rather than receiver operator curve analysis, should be employed.

(5) An important group of patients who potentially may benefit from this test are those who present with leg pain which is

not because of arterial disease. Unfortunately no normal (i.e. asymptomatic) controls were included in this study, so it is not clear how the test will perform as a primary diagnostic or screening procedure. In addition, no reproducibility data were presented, making it difficult to assess whether the mediocre diagnostic accuracy was the result of physiological variation, operator technique or flawed design.

(6) The combined use of duplex ultrasonography, a video recorder and Doppler waveform processing can hardly be described as a 'fast simple test'. As resting and hyperaemic flow waveform parameters can be expressed as angle-independent dimensionless ratios, such measurements could be more easily obtained with one of the commercially available, bidirectional continuous wave Doppler instruments, and would free the duplex machine for patients who do require it

The development of new diagnostic tests requires a careful phased approach in which the appropriate patient population is identified, sources of diagnostic error are minimized and the necessary equipment and personnel are defined[13]. Given the evidence presented here, I am forced to disagree with the authors' conclusion that this is an important advance on existing non-invasive assessment techniques.

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Authors' reply

Sir

We respond to the points raised by Mr Dodds as follows·

(1) Four patients did not tolerate our protocol of thigh cuff inflation, despite the use of wide cuffs of bladder size 20 × 50 cm. Greater pressures and durations would have had the undesirable effect of excluding more patients because of cuff intolerance.

(2) In the development of the duplex hyperaemic test, a number of easily measured Doppler criteria were studied at rest and during hyperaemia. The important feature of any test is how it performs when used in an unselected group of patients. In this respect the postocclusive hyperaemic duplex (PHD) test performed well in the prospective patients. In this group the positive and negative predictive values are important indicators of the value of this test.

(3) In patients with aortoiliac stenosis and resting pull-through pressure gradients of 20 mmHg, satisfactory balloon dilatation results in reduced gradients and improved limb perfusion. These pressure changes have been better understood since the advent of balloon angioplasty, and the references quoted predate this advance.

(4) The unsupported assertion of statistical trawling and the pejorative remark about receiver operator curve (ROC) analysis are surprising, as our ROC analyses in this area, dating back to 1980 and referenced in the paper, have previously been well received.

(5) Ankle pressure measurements before and after treadmill testing are the established primary diagnostic and screening methods and mostly rule out arterial disease in patients with leg pain which is not due to arterial disease. These areas were outside the scope of our study and we made no such claims in the paper We are disappointed that Mr Dodds feels that the study design was flawed and the diagnostic accuracy was mediocre. These criticisms were not made by the referees nor by others in the field with whom we have discussed this study.

(6) In our experience, comparable information cannot be obtained by a continuous wave Doppler.

The PHD test has the advantage of not requiring further complex equipment beyond that normally found in a modern vascular studies department Complex computer-based analysis of results is not required. We believe that the PHD test offers a fast, simple assessment of aortoiliac disease and would encourage Mr Dodds and others to try it.

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Our Statistical Adviser comments as follows:

There is little substance in Mr Dodds' criticisms. Under point (2), it is true that predictive values would not be useful measures if the 50 patients were selected as 25 cases and 25 controls However, from my reading of the paper, it appears that the 50 patients were an unselected group of patients requiring investigation, and it was coincidental that on investigation precisely 50 per cent were found to have aortoiliac disease.

Under point (4), the 'statistical trawling' is entirely appropriate. Such an approach leads to an overoptimistic impression of performance when the diagnostic rule is applied to the cases used in its derivation, as the authors acknowledge in the first paragraph of the Discussion. This problem is easily overcome, as the authors have done, by evaluating the performance of their test on a separate prospective data set. It is in fact quite irrelevant whether, as in this case, the test is derived using appropriate statistical methodology, or whether it comes from poring over chicken entrails. A prospective evaluation gives a valid, unbiased assessment of the performance of the test.

Mr Dodds' suggestion that the authors use 'some form of multiparameter cluster analysis or modelling, rather than receiver operator curve (sic) analysis' misses the point. The authors have used a multivariate technique, namely logistic regression. This goes hand-in-hand with an analysis of the receiver operator characteristic (ROC) curve, which shows the various combinations of sensitivity and specificity that may be obtained by using different cut-off values for the score derived from the logistic regression.

If there is a limitation in the authors' prospective evaluation of performance, it is that they do not give confidence intervals for the sensitivity and specificity of their test. These estimates are derived as proportions based on denominators of approximately 25, and so will lack precision. A larger sample size is required before one can be confident that the sensitivity and specificity are indeed close to 90 per cent, but the data as presented are promising.

My final comment is not really statistical, but under point (1) Mr Dodds' questions the validity of the 3-min occlusion. This is a further example of the proof of the pudding being in the prospective evaluation. Using the 3-min occlusion, the authors have developed and evaluated a diagnostic test which performs well. If Mr Dodds is correct, there might be potential to develop an even better test by refining the length of the occlusion, or perhaps the pressure.

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Two-layer closure of typhoid ileal perforations: a prospective study of 46 cases

Sir

May I comment briefly on a few aspects in the recent article by Mr Singh and colleagues (*Br J Surg* 1995; 82: 1253) who reported a mortality rate of 11 per cent for typhoid ileal perforations? They recommend 'liberal blood transfusion' to combat septicaemia and hasten wound healing. However it has now been considered imprudent and even hazardous to use blood transfusion for such reasons[1].

The contention that the addition of a second layer in closure of the perforation has lessened the chance of suture line leakage or repeat perforation is difficult to justify as single-layer closure was never tried in their series. In any case, contradictory to what the authors point out, the treatment described in most standard surgical textbooks for typhoid perforation is two-layer closure and not 'surgical plication'[2]. However it is admirable that the authors did not encounter any enterocutaneous fistula at all in their series. Early surgical intervention and adequate perioperative care must have contributed to their excellent results.

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Trauma and bacterial translocation

Letter 1

Sir

The article by Professor Saadia (*Br J Surg* 1995; 82: 1243–4) highlights the difficulty of searching for a direct relationship between bacterial and endotoxin translocation (BET), and multiple organ failure (MOF). The relationship is most likely an indirect one. There is increasing recognition of the role of gut bacteria and/or endotoxin in activating submucosal leucocytes, macrophages and the endothelium[1,2]. These activated cells produce inflammatory mediators, cytokines and products of arachidonic acid metabolism, which they release into the systemic circulation to induce changes similar to those seen in patients with MOF.

A recent study showed that concentration of the cytokine, tumour necrosis factor (TNF), increased in the portal vein of rats after haemorrhage before any increase in the systemic circulation[3]. Once in the systemic circulation, TNF may induce neutrophil sequestration, permeability and oedema of the lungs as seen after limb ischaemia–reperfusion injury[4,5]. Some of these gut-induced mediators may also be necessary for neutrophils that are activated in other organs to sequester in the lungs[6].

On the other hand, submucosal leucocytes activated or primed by bacteria go to the liver, and if the organ has a normal endothelium and interstitium, the leucocytes are arrested there until the stimuli disappear[1]. This process does not require the presence of gut bacteria or endotoxin in the portal or systemic circulation. If the endothelium is already primed, the leucocytes bind to it and migrate into tissues where they interact with local factors and cause further injury. Bacterial toxins and phagocytosis of any materials, including devitalized tissues, may amplify the system. Some of these activated leucocytes then go on to the next organ, the lungs[1]. This process was demonstrated in a rat model, where neutrophils were primed and released into circulation after sublethal gut ischaemia–reperfusion injury without causing any pulmonary damage. Introducing a sublethal dose (not enough to cause pulmonary damage) of *Salmonella typhimurium* endotoxin during this vulnerable period increased pulmonary permeability and leucosequestration[7].

While BET initiates the activation of leucocytes and other cells, other factors are necessary for the propagation and amplification of injury. For example, it seems that endothelial damage is necessary in the organs receiving activated or primed leucocytes for injury to occur[1]. The activation of endothelium and leucocytes can occur in any marginally viable wound, for example burns, crush injury and pancreatitis[1], but the gut is the most likely culprit in most injuries.

The gut, which receives 15–20 per cent of cardiac output, is more prone to hypovolaemia than other organs[8], and a fall in intestinal oxygen consumption begins when extraintestinal oxygen consumption is still independent of oxygen delivery[9]. Sepsis potentiates mild or moderate hypoperfusion, which ordinarily the gut can compensate. The explanation is that sepsis increases the demand for oxygen, reduces the ability of tissues to extract and utilize oxygen, increases short-circuiting of oxygen in the villous counter-current exchanger[10, 11] and selectively reduces mucosal blood flow[12]. All these contribute to gut damage and BET.

Because BET causes injury to remote organs in this indirect manner, and factors in these organs are necessary for further injury, it is easy to see why there is no direct relationship between bacteraemia and MOF. The other argument against the possible involvement of bacteria in patients with MOF is that antibiotic treatment does not necessarily prevent MOF. This may be because bacteria activate submucosal leucocytes to produce inflammatory mediators in the tissues before antibiotics neutralize them[2]. In splanchnic ischaemia, it is possible that antibiotics do not reach adequate tissue levels necessary to destroy all the bacteria that stimulate leucocytes. In addition, they may kill the normal anaerobic commensal, thus supporting the growth and penetration of the gut mucosa by more pathogenic aerobic species[1]

Finally, as explained by Professor Saadia, increased gut permeability and BET occur via different routes. Nevertheless, abnormal intestinal permeability may be an early characteristic of cellular damage, and it may reduce the resistance of enterocytes to exogenous antigens, which could then penetrate the intestinal barrier[13]. Rather than indicating MOF, abnormal intestinal permeability probably indicates the increased likelihood of BET occurring. Similarly, gut mucosal pH is most likely an indication only of early splanchnic ischaemia from various causes, including inadequately resuscitated gut mucosa, which is then prone to injury. Increased intestinal permeability is an early manifestation of this injury.

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Letter 2

Sir

We read with interest the excellent paper from Professor Saadia summarizing the clinical studies investigating gut barrier dysfunction after trauma. With regard to gut mucosal pH, a study of patients undergoing abdominal aortic aneurysm surgery has shown that intramucosal acidosis of the sigmoid colon was associated with translocation of endotoxin[1]. However, there was no convincing evidence that this systemic endotoxaemia affected clinical outcome[1]

Turning to the relationship between intestinal permeability and bacterial translocation, it has been shown that both intestinal permeability and bacterial translocation are increased in animal models of intestinal atrophy, sepsis and haemorrhagic shock[2]. However, no correlation was found between intestinal permeability to lactulose and translocation of bacteria in an experimental model of total parenteral nutrition-induced intestinal atrophy[3]. When considered with the evidence that translocation is a transcellular phenomenon and that permeability is largely due to paracellular penetration of much smaller molecules, it appears that these measures of barrier function are unrelated[2].

In addition to the studies described by Professor Saadia, a prospective multi-unit study of 30 traumatized patients failed to detect circulating endotoxin in any of the blood samples taken before resuscitation or in any of the serial post-trauma samples[4] Therefore, despite the obvious attractions of the gut hypothesis of multisystem organ failure[5], we would agree with Professor Saadia that the theory is not supported by the evidence that is currently available.

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Book reviews

Laparoscopic Surgery. An Atlas for General Surgeons

G. Vitale, J. S. Sanfilippo and J. Perissat (eds). 283 × 217 mm. Pp. 260. Illustrated. 1995. Philadelphia, Pennsylvania: J.B. Lippincott. £99·50.

If you want a concise book full of practical information about laparoscopic surgery that you can read, rather than a reference tome for the shelf, this is it. It does not give details of results (rapidly out of date anyway) nor overly concern itself about whether an operation should be laparoscopic or open, but it covers three areas. First, a historical and ethical section, including medicolegal considerations, is discussed by a lawyer. Second, general principles are presented, covering topics such as paediatric surgery, laparoscopy in pregnancy and management of complications, as well as many technical tips. The final part describes common operations well and without wasting space discussing pathology (unless necessary). Since pathology is the same whatever the surgical technique and is described in standard texts, why do most laparoscopic surgery books insist on repeating it? The lack of any mention of gastrointestinal endoscopy is equally welcome. The authors speak with confidence through the pages and in a most readable style. Criticisms are few: the paediatric section repeats some of the information given elsewhere and could more clearly emphasize the differences between adult and child surgery; some photographs are poor quality and the patient illustrated on the front cover appears to have dextrocardia (although, overall, the book is particularly well illustrated); a chapter on thoracic surgery could have been included. Many recent books on laparoscopic surgery are full of padding: this one is a refreshing change.

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Reducing Breast Cancer Risk in Women

B. A. Stoll (ed.). 245 × 163 mm. Pp. 248. Illustrated. 1995. Dordrecht: Kluwer Academic Publishers. £58.

This book, one of the *Developments in Oncology* series, comes from the prolific pen of Basil Stoll. There is an introduction by Susan Love, one of the political activists of breast cancer management in the USA. It contains sections on recognizing increased breast cancer risk, advising women at high risk, avoidance of possible risk factors, and a final section on perspectives and viewpoints. As such, the book provides a useful summary of risk factors and the interventions being currently evaluated. With the rapid developments in the molecular biology of breast cancer the chapters on genetic testing will soon be out of date, but they provide a useful statement of current knowledge. This is a book to dip into, and some chapters will appeal more to the breast nurse specialist or counsellor than the surgeon. As such, this book will be useful for breast cancer units.

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Surgical Infections

D. E. Fry (ed.). 285 × 220 mm. Pp. 787. Illustrated. 1994. Boston, Massachusetts: Little Brown Company. £70.

Serious bacterial infection is gratifyingly rare in a contemporary surgical practice, but this excellent book covers all aspects of aetiology, prevention and management in a thorough and readable style. The chapters are concise and digestible, written by a variety of American authors although Dr Fry, the editor, has done the lion's share. He is to be congratulated on his editing which ensures that the book has good continuity of style and is clearly and well referenced. The first 100 pages are devoted to the basics in surgical sepsis: aetiology, prevention, antiseptics, antibiotics etc. The middle section relates to specific infective scenarios, and surgeons will find comprehensive coverage relating to problems in their own particular specialty. The final 100 pages cover contemporary topics, such as immune modulation, and details and causes of the sepsis syndrome. While reviewing the book I was able to obtain helpful advice on breast abscesses (a debate with the senior house officer), pseudomembranous colitis, necrotizing fasciitis (an infamous Gloucester problem) and my once-in-a-lifetime ruptured mycotic aortic aneurysm. The chapter on mycotic aneurysm was a treat; the author reviewed 139 case reports from the literature and deserves a bonus for his efforts. In summary, this is, I suppose, a library book. Its scope and tapestry are too broad for any individual surgeon, but I have enjoyed and profited from it and will doubtless find it useful in the future.

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Recent Advances in Surgery – 18

I. Taylor and C. D. Johnson (eds). 233 × 156 mm. Pp. 258. Illustrated. 1995. Edinburgh: Churchill Livingstone. £27·50.

This is the 18th *Recent Advances in Surgery* and is another excellent text in the series. The chapters are up to date, well written and generally well referenced. That on pancreatitis is particularly well written although a minor criticism would be the quality of *Fig. 1.2b*. The chapter on non-biliary laparoscopic surgery is good and well referenced, although a chapter such as this becomes quickly out of date in such a rapidly advancing field, and I am sure the editors will want to re-tackle this topic in the next year or two. The chapter on screening for colorectal surgery is useful, particularly for those candidates sitting forthcoming examinations. The text on parathyroid surgery by Tony Goode is excellent, well written and authoritative. There is also an excellent chapter on the critically ischaemic limb, although within a few years this may need to be updated when the niche for vascular stenting is more defined. The text by Kingsnorth on modern hernia management is topical and well presented. The coverage of monoclonal antibodies and lasers is useful for examination candidates, although the quality of *Fig. 12.5* is not particularly clear. The book ends with the usual recent advances in general surgery — a literature review by Taylor — and this is again up to date and authoritative. In summary, this is an excellent book for both the trainee and established surgeon. It should be purchased for his or her personal library.

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Organ Shortage: The Solutions

J. L. Touraine, J. Traeger, H. Bétuel, J. M. Dubernard, J. P. Revillard and C. Dupuy (eds). 245 × 165 mm. Pp. 381. Illustrated. 1995. Dordrecht: Kluwer Academic Publishers. £92·25

This book contains summaries of the oral presentations and posters of an international conference in Lyon in June 1994, on the subject of the shortage of donor organs. There are 41 oral presentations and 41 posters covered The poster presentations are simply photocopies of the abstracts submitted to the meeting by relevant authors. Although the book is divided into logical sections such as *Expanding the donor pool* and *Optimization of organ procurement*, the various contributions inevitably stand in isolation and it is not, therefore, the sort of book that can be picked up and browsed through. The advantage of a rapidly published text of this nature is that it contains up-to-date information from experts in the field. I found the contributions on the effect of transplantation laws and organ procurement, and the associated psychological dimensions in donor refusal, particularly well written and interesting. The majority of the articles are well presented and referenced; illustrations are of a high standard. For the reader requiring an up-to-date reference book on the numerous aspects of organ donation, this text represents an excellent purchase. For the reader who is relatively new to the field and requires a more structured read, there are alternative texts which better fulfil that role.

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Surgery: A Problem-Solving Approach. 2nd ed.

J. H. Davies, G. F. Sheldon, W. R Drucker, D. S. Gann, R. S. Foster Jr., E. E. Moore, R. L. Gamelli and B. A. Pruitt Jr. (eds). 285 × 220 mm. Pp. 2477. Illustrated. 1995. St Louis, Missouri: Mosby.

Q & A Review of Surgery

R. L. Gamelli, R. S. Foster Jr. and E. E. Moore (eds). 228 × 154 mm. Pp. 235. Not illustrated. 1995. St Louis, Missouri: Mosby. Both for £99.

This multiauthor textbook aims to provide basic science explanations for disease processes and to apply the theory to the understanding of the resolution of clinical problems by surgeons. I found this approach both enlightened and useful. Each chapter is generally well researched and authored by internationally recognized authorities in their field. The two volumes cover the whole field of general surgery as well as cardiothoracic and paediatric surgery, neurosurgery, and head and neck surgery. Aimed primarily at trainees preparing for examinations, the book also provides a useful reference for the established consultant. To help the trainee reinforce his/her learning, a 'Questions and Answers' paperback book is provided with the volumes to allow revision of the main points in each chapter by multiple choice questions. This provides an innovative way to reinforce the important points from each chapter and ensure they have been digested by the reader. There is a review table at the end of each chapter dealing with clinical problems to enable the reader to quickly get hold of the take-home message. Occasional gaps exist, e.g. apoptosis is not discussed, but this should not detract from the excellence of the overall contents. Although the book is competing with the *Oxford Textbook of Surgery*, which has the advantage of being a transatlantic venture compared with this all-American textbook, both volumes are good value for money. I am certain that *Surgery: A Problem-Solving Approach* will become a standard reference textbook for surgeons and deserves to be in any surgical library.

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Notices and announcements

26 February–1 March 1996
Basic Science for Orthopaedic Surgery
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

18–22 March 1996
An Update in Surgery for General Practitioners
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

22–23 March 1966
Neuroendocrine Tumor: New Biological and Clinical Aspects
Turin, Italy
Information: F. Orlandi and P. Paccotti, Clinica Medica Generale, Azienda Ospedaliera San Luigi Gonzaga, Regione Gonzole 10, 10043 Orbassano, Torino, Italy

22–24 March 1996
5th Biennial Meeting of the International Society for Applied Cardiovascular Biology
Manchester, UK
Information: M. G. Walker, Department of Vascular Surgery, Manchester Royal Infirmary, Manchester M13 9WL, UK

28–29 March 1996
Measurements in Wound Healing
Southampton, UK
Information: G. Kennedy, IPSM Meetings and Exhibitions, 4 Campleshon Road, York YO2 1PE, UK

31 March–3 April 1996
Trauma and Critical Care – 1996
Las Vegas, Nevada, USA
Information: Carol Williams, Trauma Department, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611, USA

1–2 April 1996
Injury Research Group Annual Meeting
Manchester, UK
Information. Dr R. N. Barton, North Western Injury Research Centre, Stopford Building, Oxford Road, Manchester M13 9PT, UK

1–2 April 1996
Congres Francophone de Coelio-Chirurgie
Deauville, France
Information: J. P. COM, CID BP 171, F14800 Deauville, France

3–5 April 1996
1st World Conference on the Prevention and Treatment of Caustic Oesophageal Burns in Children
Izmir, Turkey
Information. Professor O. Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, TR-35100 Izmir, Turkey

6–8 April 1996
7th Annual Scientific Conference — Current Concepts in Thyroid Disease
Doha, Qatar
Information: Dr A. A. Gahani, P O. Box 3050, Doha, Qatar

10–12 April 1996
96th Annual Congress of the Japan Surgical Society
Chiba, Japan
Information: K. Isono, Department of Surgery II, Chiba University School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260, Japan

11–12 April 1996
Endovascular Aortic Aneurysm Surgery
Nottingham, UK
Information: B. R. Hopkinson, Consultant Surgeon, University Hospital, Nottingham NG7 2UH, UK

14–18 April 1996
26th Biennial Congress of the International Society of University Colon and Rectal Surgeons
Lisbon, Portugal
Information: TOP Tours, Congress Department, R Luciano Cordeiro, 116–1050 Lisboa, Portugal

18–19 April 1996
Femoro-Distal Workshop
Bath, UK
Information. Mrs K Cox, Secretary to Professor M Horrocks, Department of Surgery, Royal United Hospital, Bath BA1 3NG, UK

5–9 May 1996
1st Congress of the World Association for Laser Therapy 'WALT'
Jerusalem, Israel
Information: World Association for LASER Therapy, c/o PO Box 50006, Tel Aviv 61500, Israel

7–10 May 1996
Research Methods in Surgery
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

12–15 May 1996
29th Annual Meeting of the Pacific Association of Pediatric Surgeons
Singapore
Information: Secretariat, Academy of Medicine, 16 College Road, Singapore 0316

15–18 May 1996
7th International Symposium on Pediatric Neuro-Oncology
Washington D. C., USA
Information: E. Paine, George Washington University, Office of CME, Washington D. C 20037, USA

20–22 May 1996
Trauma and Critical Care '96 - Point/Counterpoint XV
Boston, Massachusetts, USA
Information: Carol Williams, Trauma Department, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611, USA

22–25 May 1996
25th Meeting of the European Histamine Research Society
Antwerp, Belgium
Information: G. Van de Vyver, Department Geneeskunde, University of Antwerp, Universiteitsplein 1, B-2610 Antwerpen, Belgium

7 June 1996
Difficult and Controversial Issues in Vascular Surgery
Saltash, Cornwall, UK
Information: Mr S. Ashley, Vascular Surgical Unit, Derriford Hospital, Plymouth PL6 8DH, UK

12–15 June 1996
International Association of Pancreatology
Mannheim, Germany
Information: Mr A. L. Warshaw, IAP Secretary, Massachusetts General Hospital, 15 Parkman Street, WAC 336, Boston, Massachusetts 02114, USA

23–26 June 1996
4th International Congress of the European Association for Endoscopic Surgery
Trondheim, Norway
Information: Congress–Conference A/S, PO Box 7609 Skillebekk, N-0205 Oslo, Norway

26–29 June 1996
CAR'96 – Computer Assisted Radiology 10th International Symposium and Exhibition
Paris, France
Information: Professor H. U. Lemke, Technical University Berlin, Institute for Technical Informatics, Sekr CG FR 3-3, Franklinstrasse 28–29, D-10587 Berlin, Germany

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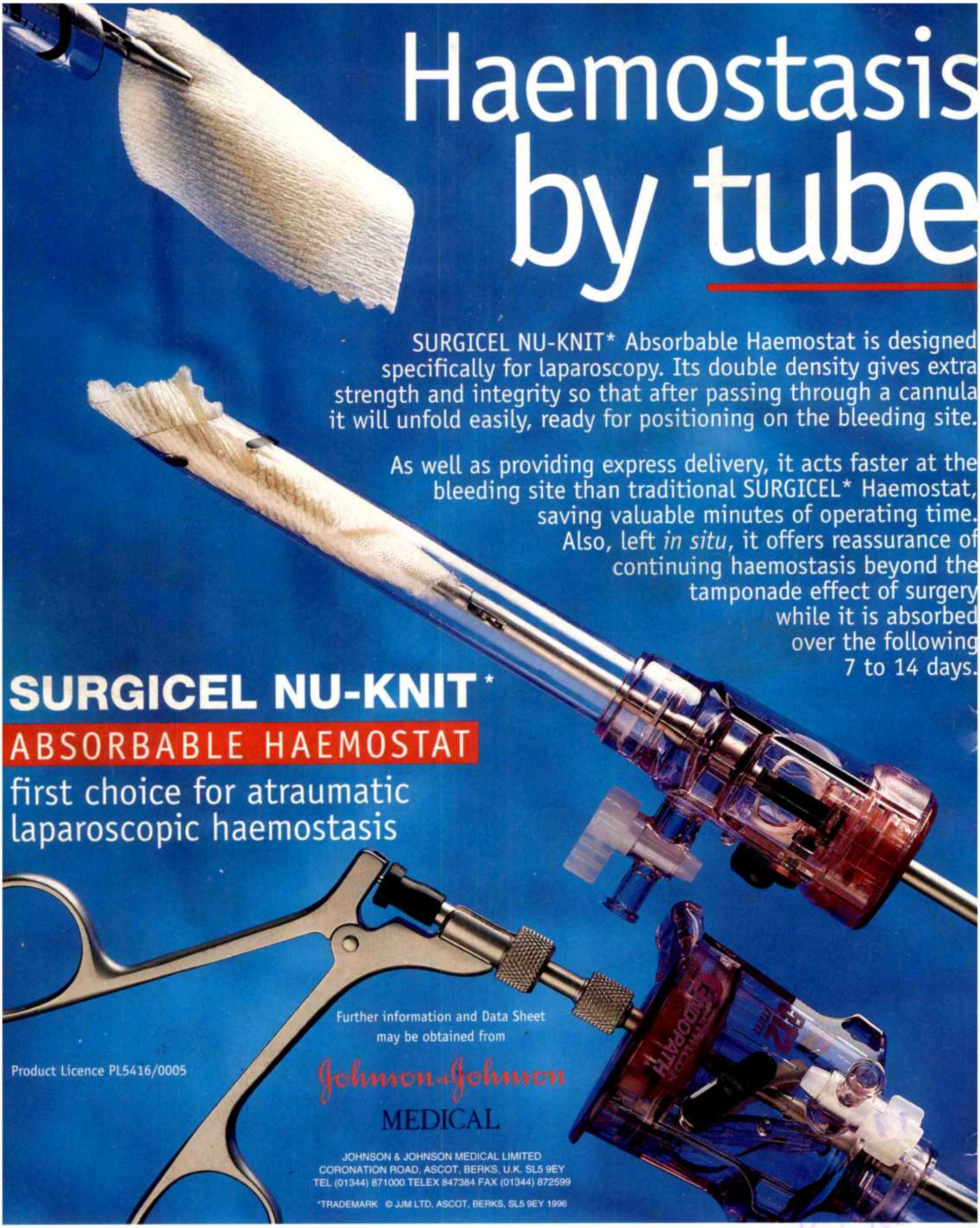

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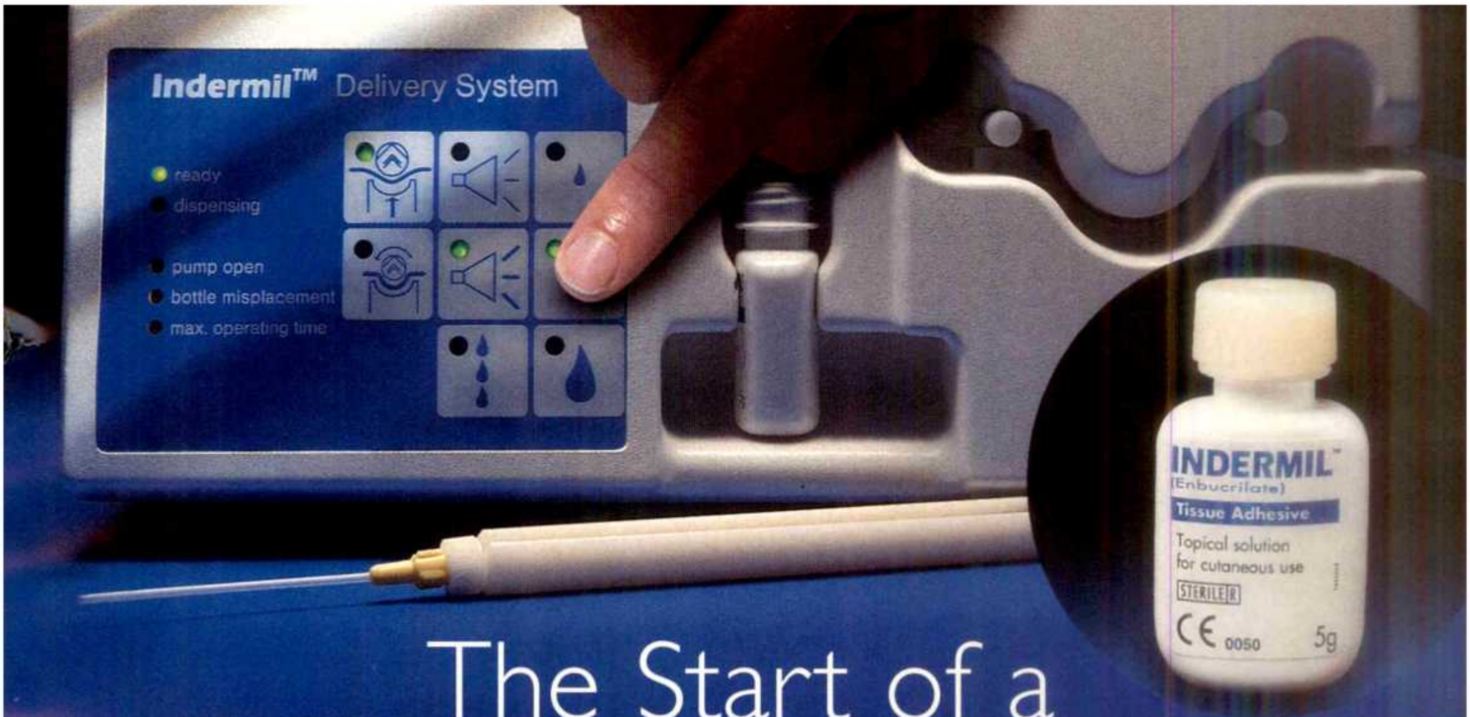

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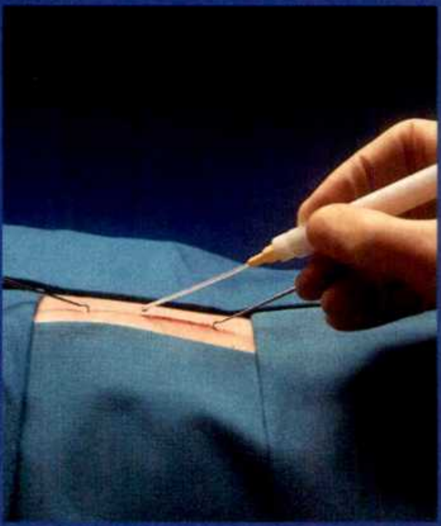

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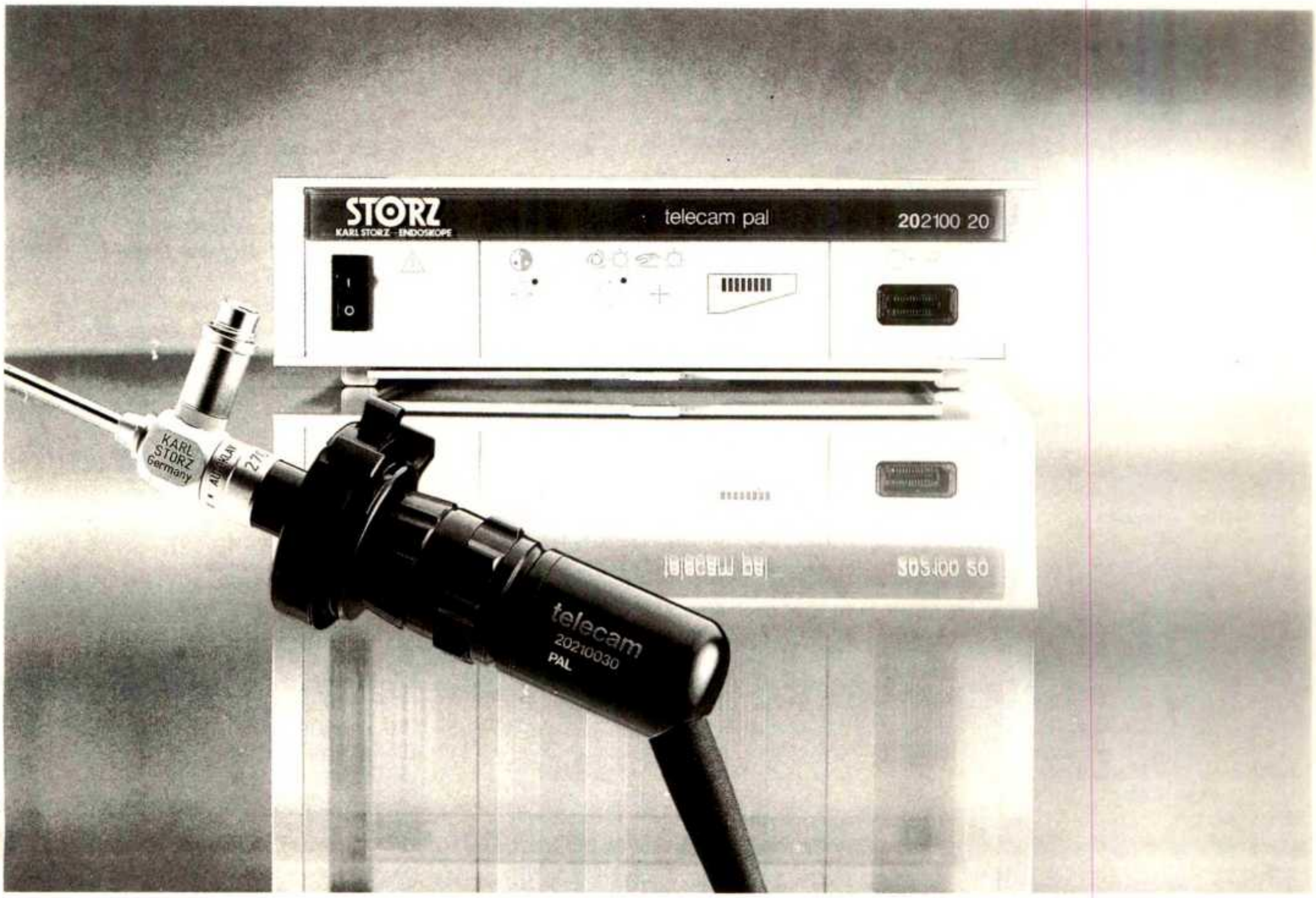

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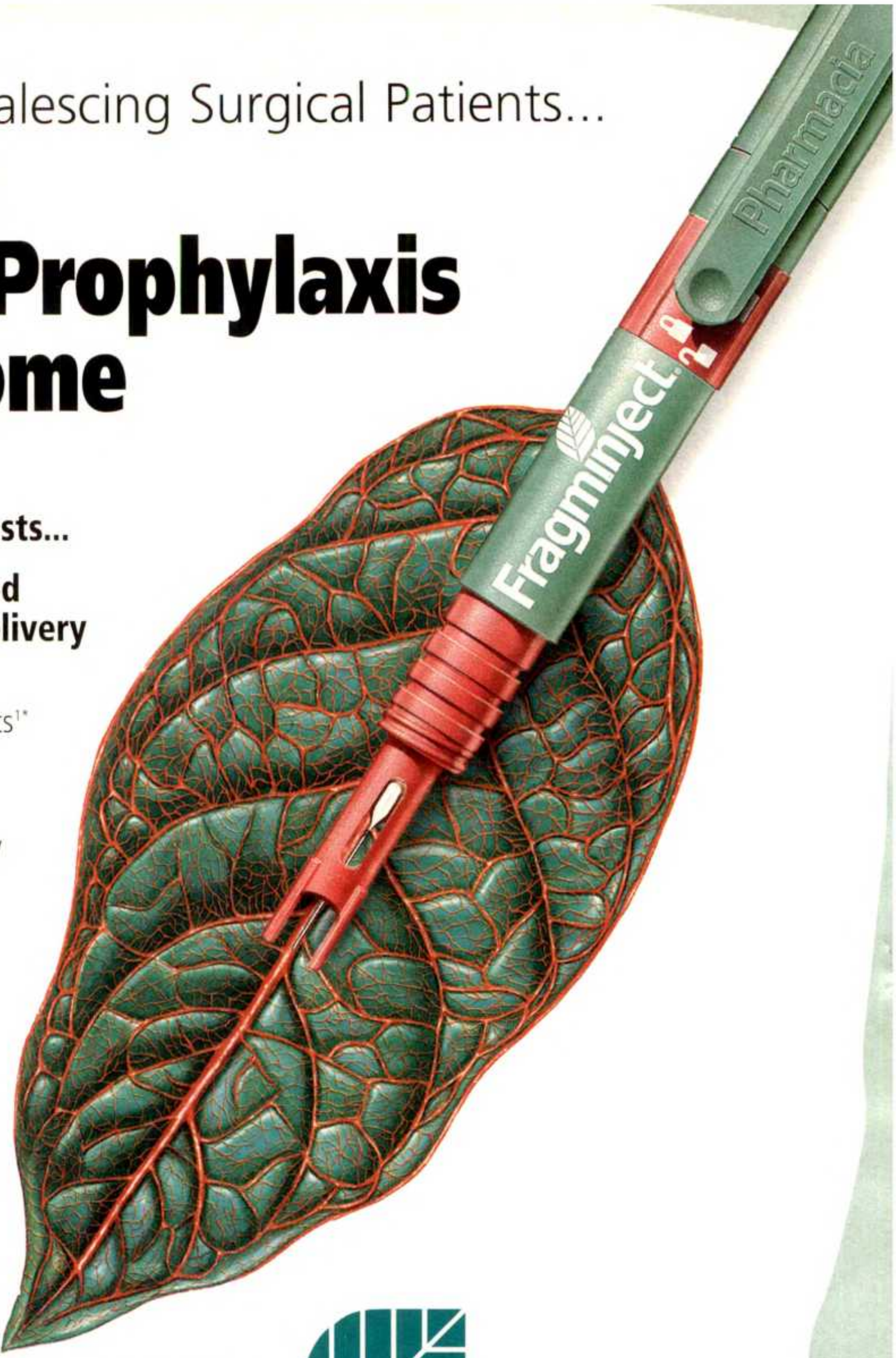

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British Journal of Surgery 1996, 83, 289–290

Leading articles

The future of surgical journals in the electronic publishing era

In 1537 James Nycholson printed the first Bible in English in the grounds of St Thomas' Hospital in Southwark. Since then, printing and publishing techniques have relentlessly become slicker and more sophisticated, but the principles have remained the same; bits of inked paper are transferred in physical form from the printer to the reader. Now at the end of the 20th century another revolution is upon us. The advent of publishing in the 15th century had to wait not just upon the development of the mechanical printing press but also the transfer of the skills of paper making from the Far East. The new revolution is also dependent on two changes. First, the evolved computer, now cheap, robust and powerful, and second, our recent ability cheaply to store and send huge quantities of data from computer to computer hither and thither across the globe by connections such as the internet.

The internet has become the darling of the media, but the information available through computer networks is currently barely more accessible to the average reader than were copies of Nycholson's Bible in the 16th century. In the UK only one home in six has a computer, in Africa almost none. Many may have seen and wondered at Nycholson's Bible but lacked the literacy to read it for themselves. Similarly, in the 1990s most surgeons remain illiterate vagrants on the margins of the new electronic environment. Let us assume though that a new generation will become computer literate and that the human-to-computer interface will become easier and quicker. What will then be the implications for surgical publishing?

First, the volume of information that can be 'published' becomes almost infinite. One benefit of this is that editors' obsession with the number and length of articles can be forgotten. Reams of raw data from experiments can be added to papers, and perhaps even case reports and negative findings might again become acceptable. The problem is that the difficult but valuable task of winnowing submitted material could disappear and editors might take it upon themselves simply to grade and edit *all* submitted work. If they do not publish material, then alternative 'publishers' of information will be able to make whatever data they wish easily accessible via the internet, at virtually no cost.

Second, the speed of information transfer will become enormous. The proposed EaSt-MAN academic network in Scotland, for example, will transfer more than two million words per minute. Even below these levels sound and high-class moving images can be transferred with text, transforming the style and value of illustration.

Third, targeted access will allow the reader to preselect topics on an interest or need-to-know basis. In theory, this should defeat the depressing omnipresence of unread journals but, by the same token, it may endanger the pleasures and educational benefits of browsing. Indisputably, though, it will allow much readier access to the information needed to answer clinical questions and hospital terminals should allow this efficient data searching to occur at the bedside.

Fourth, interactivity between the 'journal' and the reader will allow instant comment by the latter on the published material for the benefit of both the editors and subsequent readers. This instant correspondence column has the potential to supplant the current system of refereeing, because it will permit multiple ongoing peer reviews.

Fifth, availability will be enhanced. At one end of the spectrum Western readers and libraries, submerged by the sheer weight of published material, may welcome the freedom that easy access to information without the need for physical storage implies. The opposite applies in the developing world, where journals are already unaffordable and thus unread. Many developing cultures now skip the postman and go straight to the telephone; so libraries and hospitals in the third world may skip expensive journals, and plan their future information base around cheap computers fed by satellite and doubling up as tele-medicine links. If speed of publication is truly important (which I doubt), the internet allows almost the ultimate in speed; articles may be delivered to the journal, edited and refereed over the internet, and then be globally available at the moment of publication[1]. Indeed, why bother with a monthly journal when papers can be published day by day, just as soon as they are ready.

What are the implications of this for the *British Journal of Surgery* and the working surgeon? La Porte[2] in a stimulating paper predicted the death of biomedical journals, a stance roundly rebutted by subsequent correspondents[3], yet radical change is at hand and we must engage the benefits. New technologies rarely oust the old (I am writing this with a pen on paper), they rather add new benefits to old systems. Nevertheless, a time may come when paper journals become too cumbersome and expensive to survive, but that moment is not with us yet and this Journal will continue to be published in its present form for many years. In the meantime we are experimenting with new forms of electronic publishing in parallel with the traditional paper format. You may already communicate with us over the internet (internet address: bjs@blacksci.co.uk). Like other journals, we may issue our back copies aggregated onto a single CD-ROM (compact disc–read-only memory) which will not only allow easier reference but also permit the disposal of dusty old issues. We are experimenting with the importation of video and the interaction between the published material and the reader. However, it is not just editors who need to adapt and journals which must change; you, the reader, may soon need to develop your personal computing skills if the new world is not to leave you a mere bystander at the edge of cyberspace.

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1 Delamothe T. BMJ on the internet. *BMJ* 1995; 310: 1343–4
2 La Porte RE. The death of biomedical journals. *BMJ* 1995; 310: 1387–90
3 Gellert G, Pitkin RM, Longmore M, Cowie J. The death of biomedical journals. *BMJ* 1995; 311: 507–8 (Letters).

Announcement

European Surgical Fellowships

Council of The British Journal of Surgery Society is pleased to announce the availability of the first tranche of European Surgical Fellowships for 1996.

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Applications should be sent to Mr J. R. C. Sainsbury, Company Secretary, The British Journal of Surgery Society, Department of Surgery, The Royal Infirmary, Lindley, Huddersfield HD3 3EA, UK by 28 June 1996.

J. R. C. Sainsbury

British Journal of Surgery 1996, 83, 291–292

Medicolegal action following treatment for varicose veins

Procedures for the treatment of varicose veins are among the commonest in surgical practice. Although major complications are rare, they may be life threatening. Minor complications are common and may give rise to grievances, particularly as patients often seek treatment for cosmetic reasons.

Reviews of the complications of varicose vein treatment in the literature allow the reader an overview of the range of injuries which may be caused; they do not deal with the progression of these adverse events to medicolegal action[1,2]. Reports of claims made following the treatment of varicose veins feature regularly in the medicolegal literature, but they usually relate to only one or two recent cases[3–5]. Nevertheless, it is clear even from these accounts that 'actionable' injuries continue to occur on a regular basis and that the same types of injuries are repeated year after year. In the UK, on average 34 patients *per annum* begin legal action against their medical attendants in connection with the treatment of varicose veins, on a background of an estimated 100000 procedures performed. Most commonly, action is begun by young women for complications relating to surgery rather than sclerotherapy. Some of these complications are serious and include instances of femoral artery stripping, ligation and division of major vessels, and division or avulsion of major nerves. Often long-term disability follows such events and the initiation of legal action against the surgeon or hospital can be easily understood.

Nerve damage is the most frequent of all major complications that result in legal action; it is cited in 15 per cent of cases. The commonest nerve injury, accounting for about half the cases, is to the common peroneal (lateral popliteal) nerve as it crosses the neck of the fibula. It is usually injured by attempts at blind avulsion of varices through stab incisions, and foot-drop results. Accurate assessment of the long-term outcome of these injuries is difficult, but few successful repairs have been documented. Injury to the saphenous nerve is also common and occurs principally during stripping of the long saphenous vein in the lower leg. The absolute incidence of this injury is certainly much higher than the perceived incidence, but the sensory loss produced in most patients is likely to be so minor that few will seek compensation.

Venous damage in the femoral triangle is responsible for 11 per cent of cases proceeding to legal action. Injury to the popliteal vein is rare. This is a reflection of the relative frequencies of procedures performed for varices at each site. The commonest mechanism of injury is ligation or division of a femoral vein which has been mistaken for the long saphenous vein. Non-occlusive damage is less common and usually results from trauma to the saphenofemoral junction at the time of ligation. Failure to note occlusive damage is catastrophic while immediate repair, where possible, is followed by a good outcome in most patients.

Only 2 per cent of actionable injuries involve arterial trauma. The superficial femoral, common femoral and popliteal arteries are involved in order of decreasing frequency, and repair is often successful if the injury is recognized at the time of the venous procedure.

The pattern of major neurovascular injuries reported in the medical literature and in defence organization journals suggests that they are frequently the result of poor surgical technique or inadequate knowledge of anatomy. This emphasizes the need for a thorough understanding of the anatomy of the femoral triangle, and adequate identification and display of structures during surgical procedures. There is no justification for 'keyhole' surgery in this area as damage to major nerves and vessels usually occurs through misidentification. Blind grasping with artery forceps during avulsion of varices should be avoided; elevation of the vein with a hook is probably safer.

Less common are instances of legal action taken for minor wound complications (13 per cent), perceived defects (6 per cent) and recurrence of varices (3 per cent). While a few actions over minor complications and cosmetic problems are due to failings in surgical technique, most appear to be the result of poor preoperative communication with the patient. It is interesting that actions are now being initiated for recurrence of varicose veins; this suggests that in these cases the patient's high expectations were not realistically moderated before operation by the surgeon responsible. Some more unusual complications have also been the subject of litigation. In two patients, components of vein strippers were left behind in the leg at the primary procedure and later recovered, having presented as a mass in one and a sinus in the other. Action has also been taken in three cases for alleged operation on the wrong leg and in nine for the wrong operation on the correct leg.

Sclerotherapy is by no means excluded as a cause of litigation. Of the 13 per cent of patients with complaints following sclerosant injection, most are provoked by the appearance of ulceration or discoloration of the skin at the injection site. Although other causes of sclerosant-related litigation are uncommon, there are documented cases of intra-arterial injection and nerve damage.

The grade of medical staff involved in litigation in the UK is obscured by Crown Indemnity and the institution of action against the consultant in charge rather than (or perhaps as well as) the junior who carried out the operation. It is clear, however, that there is a fairly even distribution of legal action across all grades, and that senior staff are by no means immune to complications, both major and minor. It is worth considering that patients awaiting treatment for varicose veins form the bulk of many general and vascular surgical waiting lists and, as such, are the target of National Health Service waiting list initiatives. In such circumstances the responsibility for operation may devolve to inexperienced junior staff. Preoperative assessment may amount to no more than a hasty clinical examination and the lowest priority is often allocated on the operating list.

As surgeons, we can hope only to minimize the likelihood of legal action; we shall never eliminate it completely. The treatment of varicose veins should be carried out by those who have been properly trained in the preoperative investigation and treatment of the disease, and who can communicate to the patient a realistic expectation of outcome in the light of previous results. A reduction of complications resulting from misidentification and lack of anatomical knowledge may be achieved by proper training of junior staff – increasingly difficult as the hours available for training diminish. Whatever the future holds, we must certainly discard the notion, commonly held, that the treatment of varicose veins is straightforward, safe, and appropriately left for inexperienced junior staff to cut their teeth on.

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Review

Surgical management of locally recurrent rectal cancer

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The surgical management of locally recurrent rectal cancer may involve major procedures and is not for the faint-hearted. Nevertheless, such treatment is preferable to chemotherapy and radiotherapy; the latter will fail over a period of months during which the patient is likely to experience intractable pain. Radical surgery offers good palliation and a better quality of life. Survival is prolonged by such operations which may be curative in up to one-third of patients. Nevertheless, surgeons must be realistic in their assessment of and discussions with patients.

Local recurrence of rectal cancer occurs in up to 30 per cent of patients after apparently curative resection and represents a significant problem. Such recurrence often occurs within 2 years of the original surgery in patients who are otherwise well and often free from hepatic or disseminated disease. Although chemoradiation reduces the risk of local recurrence and palliates many patients with recurrent disease, it is not curative. The rate of survival of patients with local recurrence of rectal cancer is less than 4 per cent at 5 years without surgical intervention and the median life expectancy is 7 months[1]. Most will die slowly with isolated, that is pelvic, disease. Centrally important is the observation that more than 50 per cent of these patients have disease that is technically amenable to surgical resection and a more aggressive policy of management is indicated than has hitherto been practised.

The purpose of this review is to discuss the factors that predispose to local recurrence of rectal cancer, the methods that can be used to detect recurrence at a relatively early stage and the therapeutic options available.

Incidence of local recurrence of rectal cancer

Local pelvic recurrence of rectal cancer occurs in between 3 and 32 per cent of patients who have undergone 'curative' resection (*Table 1*). This wide range in the reported incidence is attributable in part to variations in quality and length of follow-up, methods of diagnosing and confirming recurrence, numbers of patients studied and to whether and how often post-mortem examinations were performed. The true rate of recurrence is, indeed, difficult to ascertain. Ideally, all patients in these reported series should have histologically proven recurrence but in practice this is never possible or indeed appropriate. After abdominoperineal excision of the rectum, it is not uncommon for there to be strong suspicion of recurrence but for accessibility to the pelvis to be restricted, except by computed tomography (CT)-guided needle biopsy, and therefore tissue diagnosis to be impossible to obtain.

Many factors affect the risk of recurrence:

Characteristics of the primary tumour

Most factors known to adversely influence survival have a similar effect on local recurrence. The more advanced the Dukes stage, the more likely rectal cancer is to recur. In one large series of patients who had undergone abdominoperineal excision of rectum, the local rates of recurrence were 9·1 per cent for Dukes A, 16·7 per cent for stage B and 40·8 per cent for stage C disease[24]. Other authors have confirmed the association between Dukes stage and the likelihood of recurrence. Not surprisingly, the extent of invasion beyond the rectum affects recurrence, with an incidence of 0·9 per cent in patients in whom no local extension was noted, compared with 5·9 per cent in patients with minimal spread and 16·8 per cent in those with more extensive spread[9]. Local recurrence is also more likely with tumours in the lower third of the rectum (14·5 per cent) than in patients with tumours in either the middle third (8·3 per cent) or upper third (5·2 per cent)[9]; this is presumably related to impaired ability to excise widely in the depths of the pelvis. The size and shape (exophytic *versus* non-exophytic) of the tumour, the presence or absence of lymphatic, venous or perineural invasion[25], the presence of obstruction or perforation of the tumour together with degree of tumour differentiation, and the presence of fixity of the tumour all influence the risk of local recurrence adversely[26]. Local tumour recurrence is twice as common in patients with non-diploid rectal carcinomas[27]. Aneuploid tumours[27] and the presence of sialomucin at the margins of the tumour[28] also have an adverse effect on recurrence and survival.

Operative factors

Extent of resection. Inadequate removal of the primary tumour is undoubtedly the most important factor determining whether the tumour recurs. Tumours fixed by malignant infiltration are more likely to recur locally than are freely mobile lesions. Microscopic involvement of the lateral margin of resection is a good predictor of local recurrence, but only if multiple sections are examined by the histopathologist; one section alone may give a false underestimate of the degree of tumour penetration[29]. The significance of involvement of the circumferential resection margin has been confirmed in a prospective study of 190 patients in which 35 of 141 specimens (25 per cent) for which the surgeon considered the resection to

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Table 1 Incidence of local recurrence of rectal cancer after curative resection

Reference	Year	*n*	Operation	Local recurrence (%)	Time to recurrence
Karanjia *et al.*[2]	1990	152	AR	2·6	Mean 12 months
Danzi *et al.*[3]	1986	93	APER	4·3	Median 11 months
MacFarlane *et al.*[4]	1993	135	AR, APER	5	84% in 3·5 years
Walz *et al.*[5]	1981	131	APER	6	73% within 3 years
Moran *et al.*[6]	1992	55	AR(DS)	7·3	Median 12 months
Heimann *et al.*[7]	1986	320	AR, APER	8·8	Median 22 months
Wilson and Beahrs[8]	1976	902	AR	8·9	n.s.
Morson *et al.*[9]	1963	1596	APER	9·7	80% within 2 years
Manson *et al.*[10]	1976	133	AR	10·5	Mean 16 months
Colombo *et al.*[11]	1987	93	AR, APER	10·7	76% within 2 years
McDermott *et al.*[12]	1985	934	AR, APER	11·5	60% within 2 years
Williams *et al*[13]	1985	140	AR, APER	11·7	75 per cent within 2 years
Pilipshen *et al.*[14]	1984	412	AR, APER	13 3	Median 19 months
Rich *et al.*[15]	1983	166	AR, APER	14·5	Median 12 months
Olson *et al.*[16]	1980	67	APER	15	n.s.
Sarker *et al.*[17]	1994	60	AR	16·7	Median 21 months
Neville *et al.*[18]	1987	373	AR, APER	19·3	Median 17 months
Vernava *et al.*[19]	1992	225	AR	21·3	n.s.
Warneke *et al.*[20]	1989	31	AR	22·6	n.s.
Rubbini *et al.*[21]	1990	183	AR	24	2 years
Mendenhall *et al.*[22]	1983	90	AR, APER	24·4	66% within 2 years
Adloff *et al*[23]	1985	113	APER	31·8	75% within 2 years

AR, anterior resection; APER, abdominoperineal excision of rectum; DS, double stapled; n.s., not stated

Table 2 Recurrence according to operation

Reference	Year	Abdominoperineal excision of rectum	Sphincter-saving resection
Williams *et al.*[13]	1985	14/74 (19)	10/66 (15)
Neville *et al.*[18]	1987	36/192 (19)	36/181 (20)
Colombo *et al*[11]	1987	6/29 (21)	12/60 (20)
Phillips *et al.*[26]	1984	57/504 (11)	67/393 (17)
Pilipshen *et al.*[14]	1984	39/142 (27·5)	66/240 (27·5)
Heimann *et al.*[7]	1986	20/118 (17)	32/202 (16)
Fegiz *et al*[32]	1994	16/55 (29)	37/70 (52·9)
Konn *et al.*[33]	1993	14/100 (14)	18/203 (8·9)
Heald and Karanjia[34]	1992	0/21 (0)	4/152 (2·6)
Tuscano *et al.*[35]	1992	5/11 (45·5)	6/13 (46·2)
Braun *et al.*[36]	1992	11/65 (16·9)	6/57 (10·5)
Amato *et al.*[37]	1991	8/69 (11·6)	9/78 (11·5)
Graf *et al.*[38]	1990	17/100 (17)	8/50 (16)
Fick *et al.*[39]	1990	4/27 (14·8)	4/32 (12·5)

Values in parentheses are percentages

have been curative had, in fact, tumour involvement of the circumferential resection margin. The frequency of local recurrence was significantly higher in patients with tumour extension to the circumferential resection margin than for those without such involvement (78 (95 per cent confidence interval 62–94) per cent *versus* 10 (4–16) per cent)[30]. Importantly, involvement of the circumferential resection margin independently influenced both local recurrence *and* survival. Therefore, wide local excision of rectal cancer is clearly important as is the need to assess the circumferential margin of resection to predict prognosis.

There appears to be no difference in the incidence of local recurrence after sphincter-saving resections, such as low anterior resection, compared with abdominoperineal excision of the rectum, as long as the distal margin of clearance is at least 2 cm[8,31] (*Table 2*). Direct comparison between the two procedures is difficult, however, as bulky tumours, particularly in a well-built man with a narrow pelvis, tend to be resected by means of an abdominoperineal approach. Although no prospective studies have been carried out to compare the outcome of patients with low rectal cancer treated by either sphincter-saving resection or abdominoperineal excision, a case–control study of very low tumours showed no difference in either local recurrence or 5-year survival rate[13].

Similarly, no *controlled* trials have tested the hypothesis that more radical surgery is associated with a reduced risk of local recurrence. Very favourable results have been reported, however, with the use of complete excision of the mesorectum, after which the risk of local recurrence in a series of 115 patients was less than 4 per cent at 4 years[40]. The cumulative probability of tumour-free survival at 5 years was 94 per cent for Dukes A, 87 per cent for stage B and 58 per cent for Dukes C lesions. The philosophy behind this technique argues that only complete excision of the mesorectum down to the pelvic floor will remove all microscopic deposits of carcinoma. How can this procedure result in a more favourable outcome than the apparently more radical procedure of abdominoperineal excision of the rectum? It may be that the latter is less radical in terms of mesorectal excision as at least part of the resection is carried out without direct vision, the specimen is manually extracted through the pelvic outlet and the perineal operator is often working with poorly defined planes, compared with the clearly defined margins around the rectum when approached transabdominally. The results obtained by Heald and Ryall[40] with this technique are impressive and should act as a target to which others may aspire.

In distinct contrast, radical dissection of the pelvic lymph nodes has not become popular. The technique is difficult to perform, especially in the obese. At present, the increased morbidity associated primarily with destruction of the sympathetic and parasympathetic pelvic nerves (incapacitating bladder and sexual dysfunction is almost inevitable[41]) does not appear to be balanced by any significant gain in terms of reduced risk of local recurrence and improved survival. Submucosal injection of gold has shown that less than 1 per cent of the lymphatic drainage from the middle and upper rectum drains to the lateral pelvic lymph nodes[42]. The lower the lesion, however, the greater is the chance of lateral nodal involvement[43]. Although some studies have suggested increased survival after radical lymph node resection in patients with Dukes B and C lesions[44], similar retrospective studies have shown no benefit[45]. The presence of extensive lymph node involvement almost always means that systemic tumour dissemination has occurred[46]. Even with extended lymphadenectomy, reported rates of local recurrence are often much higher than the rates reported by other authors with conventional resection alone[47].

A recent study[48] that compared rectal resection with and without lateral lymph node dissection showed no overall benefit although local recurrence was significantly less after extended lymphadenectomy. Local recurrence, distant metastasis and 5-year survival rates were 7, 9 and 76 per cent respectively in patients in whom extended lymphadenectomy was carried out, compared with 16, 7 and 72 per cent in those who had resection alone. Indeed, only 11 per cent of patients who underwent pelvic node dissection were subsequently found to have nodal deposits. Involved nodes are difficult to detect; one study found 78 per cent of involved nodes to measure less than 5 mm which highlights the problems with preoperative and intraoperative detection[49]. Disappointingly, very few patients will achieve long-term survival in any event if their pelvic nodes are involved with metastatic disease[41]. Patterns of recurrence, metastasis and rates of survival appear to be related more to the presence of venous or neural invasion rather than to whether the pelvic nodes are resected[48].

No-touch technique. Preliminary ligation of the mesenteric vessels with isolation of tumour between tapes has long been recommended in the resection of colorectal cancer[50] on the basis that the manipulation of tumour results in the shedding of tumour cells into the circulation[51]. These cells may have the ability to seed and grow as metastatic deposits[52]. Practically, this means early ligation of the vessels, placement of constricting tapes above and below the tumour, and instillation of a cytotoxic agent into the lumen of the bowel between the tapes. A retrospective study[50] reported a crude 5-year survival rate of 68·5 per cent with the 'no-touch' technique compared with 52·1 per cent in patients treated conventionally. Subgroup analysis showed an even more pronounced apparent benefit for patients with Dukes C disease: 57·8 *versus* 28·1 per cent. This study was flawed, however, not only by its retrospective nature but also by the fact that one surgeon's results with the no-touch technique were compared with the results of five surgeons using the conventional approach. A more recent prospective trial[53] of 236 patients randomized to the no-touch isolation technique ($n = 119$) or conventional resection ($n = 117$) found that the time taken to develop hepatic metastases was longer in the former group but that no advantage in overall survival was gained. Local recurrence after rectal excision occurred in six of 32 patients after a no-touch procedure compared with three of 26 patients after conventional resection. The phenomenon of malignant cells being released from colorectal cancers appears to occur throughout the life of the tumour and intraoperative manipulation seems unlikely to increase the magnitude of this process. Moreover, the viability and metastatic potential of the shed cells is unclear[54,55].

Level of ligation of inferior mesenteric artery. Since the original description of the upward spread of rectal cancer[56], the level at which the inferior mesenteric artery should be ligated has been the subject of much debate. Lord Moynihan of Leeds argued[57] that the tie on the inferior mesenteric artery should be flush with the aorta to remove the more proximal lymph nodes and this became an established practice. However, a large, albeit retrospective, study[58] of 1370 patients with rectal cancer found no difference in survival between the 586 patients in whom a high tie had been performed and those who received a low tie (below the origin of the left colic artery). Again, once nodes are involved at a site remote from the rectum, more proximal dissemination of disease is likely to have occurred.

Stapled versus *hand-sewn anastomosis.* A number of theoretical arguments has been put forward to suggest that stapled anastomoses are more likely to be associated with local recurrence than hand-sewn anastomoses[59,60]. A retrospective study[61] of 119 consecutive patients who had undergone potentially curative anterior resection for rectal cancer found that local recurrence of tumour was more common in patients with mid-rectal tumours with stapled anastomoses than in those with hand-sewn anastomoses: 26 *versus* 10 per cent ($P = 0.07$). No differences were seen with either upper or lower third rectal tumours. A prospective randomized study[17] found that six of the 30 patients with hand-sewn anastomoses developed local recurrence compared with four of 30 patients with stapled anastomoses. Other studies have also shown no significant difference in local recurrence after stapled *versus* hand-sewn anastomosis[13,62,63]. No significant difference in survival was observed. In contrast, a randomized study[64] of 294 patients who underwent potentially curative resection found an incidence of tumour recurrence of 29·4 per cent in the sutured group compared with 19·1 per cent in the stapled group ($P < 0.05$). This study included colorectal ($n = 109$), colocolic ($n = 73$) and ileocolic ($n = 112$) anastomoses. The authors did not state explicitly the number of *rectal* resections nor the outcome for rectal cancer as a subgroup. Spillage of tumour cells into the pelvis, intraluminal trauma and increased risk of contamination caused by the transanal passage of the anastomotic gun have been suggested as possible mechanisms by which growth of residual tumour deposits may be augmented[61]. It is more likely, however, that any increased risk of local recurrence seen with stapled anastomoses is the result of patient selection; a stapled anastomosis is more likely to be used in a narrow pelvis and the chance of an inadequate pelvic dissection and understaging of the disease is increased in such patients. Alternatively, increased use of stapling instruments may have resulted in an inappropriate abandonment of abdominoperineal excision in the management of rectal cancer.

Blood transfusion and splenectomy Blood transfusion and splenectomy have immune modulating effects and improve allograft survival after renal transplantation[65,66]. Transfusion of allogeneic blood has effects on the immune system which influence the behaviour of some tumours[67]. Patients with colorectal cancer who receive one or more units of whole blood have a significantly worse outcome than non-transfused patients[67–69]. If the adverse effect of blood transfusion is mediated by exposure to allogeneic antigens in transfused blood, then it is reasonable to suppose that such effects would be minimized by the use of autologous blood transfusion.

Elimination of the plasma fraction negates substantially the deleterious effects of blood transfusion[70]. Studies of the association between blood transfusion and recurrence of colorectal cancer have been conflicting, however, mainly because of the retrospective nature of the studies and the variety of transfusion measurements used[71–76]. Perioperative blood transfusion is more likely to be given to patients with fixed tumours and this clearly affects outcome[77]. The finding of an association does not imply causation. The apparent adverse effect of blood transfusion may be explained by the circumstances that necessitated the transfusion[78]. A trial[79] of 475 patients randomized to receive autologous or allogeneic blood found no significant difference in prognosis. The practical implications are that perioperative transfusion should only be undertaken in patients with rectal cancer when absolutely necessary and preference should be given to the use of plasma-reduced or fresh blood[80].

A logical extension to this argument is the hypothesis that the spleen may play a role in the tumour-bearing host[81]. Several investigators have demonstrated decreased growth of colorectal tumours and improved survival after splenectomy[82,83]. Such experimental studies have inherent problems including tumour cell kinetics, tissue type, immunogenicity of tumour cells, inoculating dose, and the time interval between splenectomy and induction of tumour[84]. A retrospective chart review[81] compared 57 patients who had undergone colorectal resection, who had either a concomitant ($n = 55$) or previous ($n = 2$) splenectomy, with a group of control patients matched for age, sex, and tumour grade and stage. The 5-year survival rate was significantly greater in the control group compared with the splenectomized patients: 62 *versus* 44 per cent ($P = 0{\cdot}03$). No data were given for local recurrence of disease and the number of patients with rectal cancer in the study was small. As is the case with blood transfusion, no prospective trials have been reported on the influence of splenectomy on local recurrence of rectal cancer.

Local recurrence after specific operations for rectal cancer

Anterior resection. Despite the attention given to recurrence at the suture line, local recurrence of rectal cancer after anterior resection most commonly occurs outside the bowel; extramural recurrence accounts for 80–96 per cent of local relapse[12,14]. Although spread of rectal cancer has long been considered to move in a cephalad direction, from pararectal nodes to nodes along the superior rectal artery to the para-aortic nodes, a significant proportion (20–40 per cent) also spreads laterally. Indeed, when abdominoperineal excision of the rectum was first popularized by Miles in 1908[56], he described three lymphatic zones of potential tumour dissemination that needed to be dealt with if the operation was to be curative; a zone of downward spread that involved the sphincter muscles, ischiorectal fat and perianal skin; a zone of lateral spread that involved the lymphatics of the pelvic floor muscles, peritoneum and fascia; and a zone of upward spread that included lymph nodes posterior to the rectum, in the sigmoid mesentery and the paracolic glands. When anterior resection was first introduced as a treatment for rectal cancer[85], immediate concerns were raised as to the efficacy of such a procedure in addressing the lateral and downward zones of spread. The potential involvement of lymph nodes at the periphery of the mesorectum and direct lateral invasion of the mesorectum must be taken into account when planning and executing potentially curative anterior resection. If the surgeon has a tendency to 'cone down' the resection towards the rectal wall in the region of the mid-rectum, then the extent of lateral resection may be inadequate. Heald and Ryall[40] argued that incomplete removal of the potentially tumour-bearing mesorectum is the main explanation for local recurrence. Their technique involves thorough excision of all of the mesorectum from pelvic side wall to pelvic side wall and down to the pelvic floor. Pelvic recurrence of rectal cancer may thus be an avoidable calamity and the aggressive removal of the mesorectum may represent a step forward in tackling the problem.

Suture line recurrence may actually be secondary to extramural disease growing into the bowel lumen or to an inadequate distal margin of resection. Previously, relapse of disease at the anastomosis has been attributed to the implantation of exfoliated cells[86], but there is some doubt about the viability of these cells and their ability to grow at a suture line[87]. Mucosal field change has also been suggested as a mechanism for local recurrence. The mucosa near a rectal cancer has a high concentration of sialomucins[88]. This abnormal mucosa has been associated with premalignant change[89] and local recurrence has been found more commonly in patients with significant sialomucin staining patterns at the resection margins[90]. If the cause of local recurrence is primarily related to mucosal factors, then abdominoperineal excision of the rectum would be expected to be associated with a very low risk. In fact, no such advantage is apparent. Most recurrences at the suture line are probably due to residual extramural disease and the relevance of implantation remains debatable.

Abdominoperineal excision of rectum. Since abdominoperineal excision of the rectum results in the complete removal of rectal mucosa from the pelvis, there can be little doubt that recurrence arises from residual extramucosal disease. Pelvic recurrences after abdominoperineal excision of rectum are characterized by sacral, side wall or combined patterns of involvement in 90 per cent of cases[14]. Such patterns of recurrence, combined with the fact that the tumour is often fixed to the prostate, pelvic side walls or the sacrum, have meant that this group of patients has been previously considered unsuitable for further attempts at resection.

Local therapy. An argument can be made to justify local procedures as an alternative to radical excision for the treatment of certain rectal cancers. However, their role remains controversial. For local excision to be contemplated, the tumour must be less than 3 cm in diameter, mobile, below the peritoneal reflection, well to moderately differentiated and not ulcerated[91]. Local excision can be performed by a transanal or transsphincteric approach. Excision must be full thickness. If adverse pathological findings are present in the locally excised specimen outcome is improved if patients undergo immediate rather than salvage resection when recurrence becomes clinically apparent[92]. The rate of relapse after local therapy for apparently curable lesions is about 30 per cent[93] although over 70 per cent of these patients will still have Dukes A or B tumours. If local recurrence after local excision was always amenable to standard rectal excision, then such occurrences could be viewed as simply a temporary inconvenience. Almost all such recurrences represent residual disease and success with standard salvage surgery has proved surprisingly elusive. The prognosis for patients with recurrence after local therapy is not good[94–96], with high rates of local recurrence and poor long-term survival[97,98].

Management of local recurrence of rectal cancer

Detection of local recurrence

Although most surgeons recommend surveillance of patients after resection for rectal cancer, there is no agreement about the frequency of follow-up, diagnostic modalities to be used or of the benefit to be gained by early diagnosis of recurrence. Clinical assessment is inferior to use of dedicated imaging modalities. Less than half of all recurrences are detected at the time of a clinic visit and more than half by other physicians, between visits, consulted as a result of the development of new symptoms[99].

Symptoms and signs associated with pelvic recurrence are related to the type of the original procedure performed. Invasion of the rectal lumen by recurrent disease after anterior resection will cause rectal bleeding and a change in bowel habit. Since access to the pelvis is easier after sphincter-saving procedures than after abdominoperineal excision of the rectum, detection of recurrence can be made at an earlier stage. Recurrence may be felt on digital rectal examination and biopsy performed. Persistent perineal or sacral pain is an ominous sign as is sciatica-type pain which may indicate invasion or encasement of the sacral plexus. This situation is considered a contraindication to resection by some authors[100], while others use it as a guide to demarcation of the extent of resection of recurrence[101]. Direct bladder infiltration will cause bladder dysfunction, while lymphatic infiltration leads to oedema of the lower limbs. Induration, a mass or persistent drainage from a perineal sinus may all develop after abdominoperineal excision secondary to recurrent disease.

The use of tumour markers as a means of detecting recurrent disease has been the subject of many studies in recent years. Carcinoembryonic antigen (CEA) has become the gold standard but others, such as CA 50, CA 195, CA 242 and CA 19-9, have been tried[102]. CEA has been used to indicate the need for a 'second-look' operation and, although recurrent disease has often been found (80–95 per cent), resectability rates have tended to be disappointing (30–50 per cent)[103–105]. The authors are unaware of any prospective trials of the value of CEA in directing second-look operations in patients with rectal cancer alone, as opposed to cancer of the colon or rectum. Despite the variable sensitivity and specificity of CEA estimation, it does appear to be a reasonable indicator of recurrent disease[106]. The value of repeat colonoscopy and serial serum CEA measurement was examined in a study of 112 patients[107]. Seventeen patients developed anastomotic recurrence, of whom 14 had raised serum CEA levels and 15 had endoscopic evidence of anastomotic recurrence. Disseminated disease was found on CT in seven patients and resectable localized disease was found in eight of ten patients who underwent laparotomy. Monoclonal antibodies raised against CEA and labelled with indium-111 or technetium-99m have been used in small numbers of patients to detect recurrence[108]. It still remains to be seen whether repeat measurements can be used to detect recurrence at a sufficiently early stage to allow more effective intervention.

CT and magnetic resonance imaging (MRI) are useful methods of detecting recurrent pelvic disease, since not only can images of the area be seen but also a needle biopsy can be directed into the site of presumed recurrence and a histopathological diagnosis obtained. Normal postoperative changes, especially after abdominoperineal excision of rectum, mimic recurrent disease and serial scans are of considerable benefit. Early studies[109] suggested that pelvic recurrences seen on CT were at least 5 cm in diameter and invasion of nearby organs was present in 25 per cent of cases. More recent studies with serial scans have identified smaller recurrences (>2 cm) earlier[110]. Initial reports claimed very high rates of accuracy for the detection of locally recurrent tumour, e.g. a sensitivity of 93–95 per cent[111,112], but later reports[113–115] suggested rates of 69–88 per cent. The main problem is the difficulty in detecting microscopic invasion of perirectal fat and determining the presence of metastatic foci within normal sized lymph nodes[116]. A mass of soft tissue density on CT may be due to recurrence of tumour or granulation tissue, haemorrhage or fibrosis[117]. In addition, radiation therapy may lead to streaky densities or a presacral mass[118]. Serial CT scans are more useful and any enlargement of a mass should suggest recurrence and the need for a biopsy[117]. Tumour recurrence on MRI can be difficult to distinguish from fibrosis and inflammation[119,120]. An initial report[121] suggested that fibrosis had a low signal intensity on T_1 and T_2 weighted images while tumour recurrence had a higher signal intensity on T_2 weighted images. More recent reports[119,120] cast doubt on this differentiation. Nevertheless, MRI can demonstrate the extent of a presacral mass well and guide percutaneous biopsy.

Transrectal or transvaginal ultrasonography shows great promise[122]. In a series of 85 patients followed after surgical excision of rectal cancer, 22 patients developed local recurrence, all of whom were identified by endosonography. Small extrarectal recurrences may be detected before there is evidence of luminal recurrence[123,124]. The five ultrasonic layers are visible in the neorectum as in normal rectum and the presence of staples does not appear to interfere with interpretation. Local recurrence of tumour has an echo-poor appearance and the degree of invasion can be assessed by the degree of disruption of the ultrasonic layers. An examination about 10–12 weeks after operation establishes a baseline, as organs such as the uterus and loops of bowel may fall to either side of the neorectum and be identified mistakenly as recurrent tumour[122]. Detailed examination of the pelvis with endoultrasonography yields additional information with which to plan further management, particularly if used in conjunction with endosonographically directed transperineal biopsy[122]. Its limitation, as for CT, is the persistent difficulty in differentiating between normal and abnormal lymph nodes[125].

Finally, detecting radiolabelled monoclonal antibodies with a hand-held gamma-counter probe appears to be of some help in intraoperative decision making at the time of second-look surgery; unnecessary resections can be avoided and the extent of potentially curative resections may be expanded. A multicentre study[126] of radioimmunoguided surgery in 98 patients found that the tumour was localized in 63 per cent of those with recurrent disease. One-third of patients with resectable disease were found to warrant more extensive resection than would have been carried out after traditional assessment. Indium-111 CYT-103 monoclonal antibody immunoscintigraphy was used in a study of 19 patients suspected to have recurrent colorectal cancer[127]. Six patients had undergone 'curative' excision of rectal cancer. Immunoscintigraphy revealed the site of recurrence in all six, three of whom were suitable for resection. Immunoscintigraphy has fared well in the detection of pelvic recurrence, achieving a rate of 74 per cent compared with 57 per cent for CT[128]. Retroperitoneal nodal uptake displays a distinctive pattern and normal sized lymph nodes with deposits of tumour will often be positive[129]. The exclusion of patients with unresectable disease as judged by radioimmunoguided surgery will result in better long-term survival rates for those in whom resection is carried out[130].

Surgical strategies

Up to 50 per cent of recurrences of rectal cancer represent strictly local failure of primary treatment. The patient is often otherwise healthy with a technically resectable tumour. The therapeutic value of reoperation in these cases has been hard to assess because of the widely held nihilistic view that surgical treatment of these patients is of no value. However, aggressive surgical management is warranted because of the appalling symptoms of uncontrolled pelvic malignancy, especially pain and tenesmus, for which radiotherapy provides only temporary relief[131]. Patients also have to cope with the odour of exposed and necrotic tumour and the distress of tumour fungating through the perineum. The nursing problems can become insurmountable and patients may survive in this state for several months[12]. Furthermore, 25–50 per cent of patients are found at post-mortem examination to have cancer limited to the pelvis at the time of death. Local recurrence of rectal cancer is not necessarily an indication of systemic disease as it is in many other cancers. The combination of clinical history, physical examination, biochemical tests and imaging modalities will identify a proportion of patients who are suitable for resection. In addition, recognition of the value of adjuvant external beam radiotherapy in Dukes C rectal cancer means that a significant proportion of these patients will already have received maximum amounts of external beam radiotherapy. What then are the surgical options available?

Local recurrence at and around the anastomosis. Most such recurrences probably represent technical failure to obtain adequate resection margins at the time of the original operation. Resection of the anastomosis, with a sphincter-saving procedure if possible, is appropriate in the absence of fixity to nearby structures. The lateral planes of dissection described for abdominoperineal resection and standard pelvic exenteration are appropriate for a centrally placed or intramural recurrence. Improved margins may be obtained with entry into a fresh surgical plane by dissection in a plane lateral to the hypogastric vessels. Patients in whom the recurrence is isolated to one side after anterior resection may be suitable for *en bloc* resection of the rectum, a portion of the bladder and the dilated ureter. The transected ureter is then reimplanted into the reconstructed bladder. Tumour that is fixed to the sacrum or pelvic side walls requires composite abdominosacral resection.

Isolated perineal recurrence after abdominoperineal excision of the rectum. Perineal recurrence of adenocarcinoma of the rectum after abdominoperineal excision of the rectum presents initially with a vague sense of perineal discomfort when the patient is sitting. The pain may become lancinating, or dull and persistent, and the patient may herald his complaint by appearing with a cushion in hand. Variable degrees of induration or a mass may be evident. Some authors recommend random needle biopsy of the perineal scar if such pain develops, even in the absence of a mass[132]. Truly isolated perineal recurrence after abdominoperineal excision of the rectum may be suitable for local wide excision. Some palliation may be obtained but cure is rare[133]. Re-excision of the area with access gained through a transverse incision at the sacrococcygeal junction gives a median survival of 12 months but no cure[134]. Perineal deposits are usually associated with tumour sited deeper in the pelvis, and local excision often results in wounds which fail to heal and enterocutaneous fistulas[135].

Anterior pelvic recurrence. Anterior recurrences confined to the neorectum and anterior organs, such as bladder, prostate, vagina or uterus, are amenable to standard exenterative procedures with *en bloc* resection of the tumour and involved organs. Such exenterative surgery for primary pelvic cancer has been the subject of debate for many years but it does provide another option for patients with local recurrence of rectal cancer[136]. It is important to resect all pelvic disease and to achieve adequate disease-free margins[137].

Total pelvic exenteration, while not terribly appealing, improves the quality of life of such patients[136]. Although exenteration has not previously been shown to yield significant benefit, this is probably because many reported series included patients with tumours fixed to the sacrum who would now be treated with combined exenteration and sacrectomy. If patients are selected carefully, pelvic exenteration is associated with a median survival of 21–30 months[136,137] and a 5-year survival rate of up to 50 per cent[137–139].

The problem with locally recurrent disease, as opposed to locally extensive *primary* disease, is that with recurrence the anatomical tissue planes have already been distorted, and disease-free margins are difficult to determine and maintain at dissection. The presacral space and the cephalad levator ani muscles have been dissected previously at the primary operation and recurrence may have invaded these planes. Resection of recurrent disease must obtain wide margins posteriorly and laterally if cure is to be obtained. If this cannot be achieved with pelvic exenteration alone then composite resection with sacrectomy will be required.

Composite abdominosacral resection for recurrent rectal cancer that involves sacrum or pelvic side walls. A rectal carcinoma with local involvement of nearby organs has a worse prognosis than one confined to the rectum[140]. A number of studies support the concept that attempts should be made to resect a tumour widely even if it appears to invade adjacent structures. The indication for posterior exenteration for rectal cancer, with preservation of the bladder, is the presence of locally advanced disease with presumptive involvement of adjacent organs[141]. *En bloc* resection of one or more organs in association with rectal carcinoma has been reported with an operative mortality rate of 8 per cent and a 5-year survival rate of 32 per cent[140] and, in a separate report, a rate of local recurrence of 16 per cent and cancer-specific 5-year survival of 62 per cent[142].

Pelvic exenteration for recurrent rectal cancer has been associated with disappointing results[14]. Many of the failures resulted from fixity of tumour to the sacrum or pelvic side walls. The feasibility and safety of combining sacral resection with pelvic exenteration has been shown by several authors[143–145]. The procedures involved are summarized below.

Clinical examination before operation needs to include assessment of the neuromuscular function of the lower limbs to identify any deficit that may be related to the tumour. Rectal and/or vaginal examination will assess size of the tumour, fixity to the lateral pelvic walls and the sacrum, and involvement of anterior organs, such as the bladder and uterus. Synchronous or metachronous tumours in the residual large bowel should be identified with colonoscopy or flexible sigmoidoscopy and barium enema examination. Plain films of the lumbosacral spine and a bone scan are useful to exclude upper sacral marrow involvement which would render the tumour inoperable[146]. CT of the pelvis and abdomen, with guided biopsy, is essential, while MRI in the sagittal plane is useful to identify the depth and level of sacral involvement.

If the patient received no adjuvant radiotherapy after the original resection, then external beam radiotherapy is given before further surgery with a dose of 5000 cGy in 20–25 fractions by continuous infusion of sensitizing 5-fluorouracil (750 mg per m^2 per day)[143]. Alternatively, with a previously irradiated pelvis, external beam irradiation should be reduced to 2000 cGy in divided fractions.

Any extrapelvic disease is identified at laparotomy. If present, a decision is made about the value of resection for palliation. The presacral plane is entered and developed to a point below S2. If tumour is found to invade S2 on frozen-section analysis, the patient is deemed inoperable[145]. The sacrum is cleared 2 cm above the tumour to prepare it for later division but no attempt is made to mobilize the tumour off the sacrum. If access is very difficult then the central pubis may be divided and the bony ring of the pelvis spread apart with a rib retractor[147]. As the bladder is mobilized, obturator nodes are swept medially with the specimen. A urinary conduit and colostomy are constructed and pedicled omentum mobilized for use in lining the raw pelvis.

Posterior procedures are performed with the patient in the prone jack-knife position. The sacrum is exposed and excised (*Figs 1* and *2*). The large perineal defect which results is closed with a rectus abdominus flap.

Radiotherapy may be given at operation. Intraoperative electron beam radiotherapy (IORT) has the advantage of being localized tumour-directed therapy which reduces exposure of normal tissues. It is delivered as a single fraction, the dose of which is determined by the adequacy of the tumour resection margins[148]. Five-year actuarial local control and disease-free survival rates in 32 patients after sacrectomy with clear surgical resection margins were 42 per cent and 33 per cent respectively[149]. IORT may be of particular benefit in patients with involved resection margins after resection of local recurrence. At the Mayo Clinic, in a series of 42 patients treated with palliative resection and IORT, there was a 3-year survival rate of 43 per cent and 5-year survival rate of 19 per cent[150]. Few centres, however, have the capability to carry out IORT. Nevertheless, the isotope palladium-103 is currently under investigation for use as a permanent implant[151], as well as in computerized remote after-loading brachytherapy techniques for pelvic irradiation boosting, which may be more practical approaches than IORT[152].

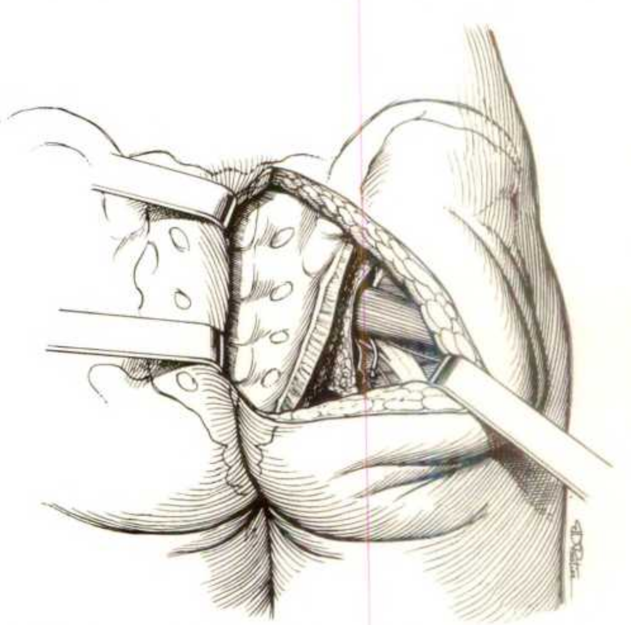

Fig. 1 The sacrum is exposed and the sciatic nerve and piriformis are identified

Resection of pelvic recurrence of rectal cancer can be carried out safely and long-term survival is expected in one-third of patients (*Table 3*). Patients with preoperative CEA levels of less than 10 mg/ml have a survival rate of about 45 per cent, while those with CEA levels in excess of 10 mg/ml have a survival rate of about 15 per cent[154]. Bone marrow invasion, involvement of resection margins by tumour and metastatic deposits in pelvic nodes are all associated with a worse prognosis[154]. Preoperative demonstration of bone marrow involvement or intraoperative demonstration of lateral pelvic nodal involvement are, therefore, contraindications to resection.

It is clearly difficult to compare the quality of life of patients with recurrent cancer with the experience of patients undergoing such major surgery, with its associated morbidity and risk of later recurrence. On balance, however, the risks of a composite abdominosacral resection can be justified by the marked improvement in the quality of life of those who, before surgery, were chronic invalids[145]. In addition, cure may be expected in about one-third of patients. Most general surgeons are uncomfortable with aggressive pelvic exenteration with bony resection, and for this and other reasons a team approach seems to work well, with involvement of urologists, plastic surgeons and even orthopaedic surgeons. The procedure should not be

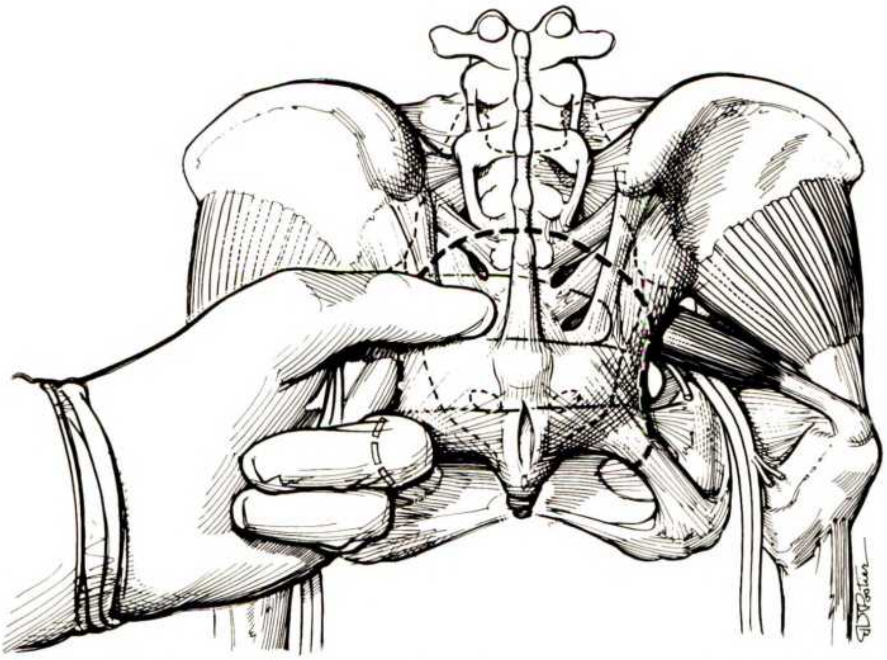

Fig. 2 The surgeon's fingers are inserted beneath piriformis and through the endopelvic fascia to reach the anterior surface of the sacrum. The level of transection of the sacrum, sacrospinous and sacrotuberous ligaments is indicated (– – – –)

Table 3 Exenterative surgery for recurrent disease

Reference	Year	*n*	Curative/ palliative	Operative mortality rate (%)	Operative morbidity rate (%)	Survival	Local recurrence (%)
Pearlman[153]	1993	41	25/16	5	44	38% at 5 years	37
Benotti *et al.*[144]	1987	29	15/14	3	25	80% at 1 year	54
Wanebo *et al.*[143]	1992	47	41/6	8·5	n.s.	24% at 5 years	
Wanebo *et al.*[154]	1994	53	47/6	8·5	38 (wound infection or separation)	33% at 4 years	18
Takagi *et al.*[155]	1986	7	7/0	0	28	4 of 7 alive (3–36 months)	28
Temple and Ketcham[145]	1992	9	9/0	9	n.s.	18% at 5 years	55
Hoffmann *et al.*[156]	1993	19	19/0	0	n.s.	40% at 5 years	42
Touran *et al.*[157]	1990	12	12/0	0	35 (urine incontinence/ retention) 25 (wound disruption)	63% at 1 year	41
Tschmelitsch *et al.*[158]	1994	20	9/11	0	10	Palliative 17 months* Curative 35·5 months*	55
Estes *et al.*[137]	1993	16	16/0	6·2	25 (wound infection)	49% at 5 years	n.s.
Maetani *et al.*[159]	1992	35	35/0	5·7	33 (wound infection)	23% at 5 years	69

*Median survival. n.s., Not stated

underestimated, however, as it is usually time-consuming, taking 6–12 h; the transfusion requirement may be 2–12 litres. Despite this, abdominosacral excision offers the only hope for those with locally recurrent rectal cancer involving the sacrum, and there is a pressing need to identify aggressively patients who would benefit from such intervention.

Conclusion

Surgical treatment for locally recurrent rectal cancer is justified. These procedures are not for the faint of heart, but a policy of simply offering patients chemoradiation is doomed to failure. Moreover, it is a policy that will not fail quickly but rather result in the gradual deterioration of the patient with intractable pain over a period of months. Radical reoperations offer excellent palliation in terms of pain relief and improved quality of life. Survival is prolonged and cure is achieved in up to one-third of patients. Nevertheless, patients will grasp at any offer of intervention, recognizing it as their last hope; the surgeon must present a realistic picture of the expected outcome.

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Review

Glutamine

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Glutamine is the most abundant free amino acid in the circulation. It is a primary fuel for rapidly dividing cells and plays a key role in the transport of nitrogen between organs. Although glutamine is absent from conventional regimens aimed at nutritional support, glutamine deficiency can occur during periods of metabolic stress; this has led to the reclassification of glutamine as a conditionally essential amino acid. Experiments with various animal models have demonstrated that the provision of glutamine can result in better nitrogen homoeostasis, with conservation of skeletal muscle. There is also considerable evidence that glutamine can enhance the barrier function of the gut. This review concludes by discussing the clinical evidence that supports the inclusion of stable forms of glutamine in solutions of nutrients.

Glutamine is a five-carbon amino acid with two amino moieties, and accounts for 30–35 per cent of all of the amino acid nitrogen that is transported in the plasma[1]. This role of glutamine as a 'nitrogen shuttle' helps to protect the body against the toxic effects of high circulating levels of ammonia. Glutamine also has important and unique metabolic functions as a vehicle for the transfer between tissues of carbon, as a fuel for rapidly dividing cells, and as a precursor for many biologically active molecules[2]. This review commences with a fairly basic account of glutamine metabolism before reviewing the results of animal studies. Particular attention is paid to studies relating to the barrier function of the gut; loss of the barrier function of the gut is a putative component of the septic multiple organ failure syndrome. The review concludes with a discussion of the results of clinical studies.

Glutamine metabolism

Key enzymes

The key enzymes related to glutamine metabolism are glutamine synthetase and glutaminase (*Fig. 1*). The greatest capacity for glutamine synthetase activity is found within the cytosol of cells in skeletal muscle and the lungs. Phosphate-dependent glutaminase is bound to the inner mitochondrial membrane where the derived glutamate is converted via glutamate dehydrogenase to α-ketoglutarate (which enters the citric acid cycle) and ammonia (which diffuses out of cells). Glutamate may also react with pyruvate under the influence of glutamic–pyruvic aminotransferase to form α-ketoglutarate and alanine. Next to glutamine, alanine is the most abundant amino acid in plasma; it is also the most important gluconeogenic amino acid[3]. High glutaminase activity is characteristic of many rapidly dividing cells[4–6].

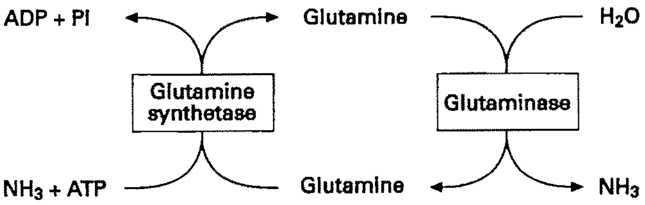

Fig. 1 Actions of the two key enzymes, glutamine synthetase and glutaminase. ADP, adenosine 5'-diphosphate, ATP, adenosine 5'-triphosphate; NH_3, ammonia; Pi, phosphate

Interorgan glutamine metabolism

Despite an intense traffic between organs, the circulating concentration of glutamine is usually maintained at a fairly constant level. As might be expected, the metabolism of glutamine varies between organs in accord with the dispersion of the key enzymes illustrated in *Table 1*.

Skeletal muscle. Sir David Cuthbertson commented in 1932 on the increased protein wasting that accompanies trauma[7]. It is now appreciated that glutamine accounts for more than 50 per cent of the intracellular free amino acid pool in skeletal muscle and that this serves as a major source of glutamine during periods of metabolic stress. Kapadia *et al.*[8] found that, when animals had 50 per cent of their parenteral amino acids supplied in the form of glutamine, there was effective maintenance of intracellular glutamine levels within skeletal muscle and a reduction in the efflux of amino acids from this muscle. It has been suggested that an increase in the intracellular concentration of glutamine within skeletal muscle

Table 1 Some generalizations about glutamine metabolism within specific tissues

Glutamine donors (high glutamine synthetase activity)
Skeletal muscle
Lungs
Glutamine regulator (high glutamine synthetase and glutaminase activity)
Liver
Glutamine consumers (high glutaminase activity)
Gut
Kidney

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promotes the development of polyribosomes and the synthesis of proteins[9,10].

Lungs. Like skeletal muscle, the lungs release glutamine and alanine in the postabsorptive state. The lungs obtain the required substrates from the circulation; more than 80 per cent of the total glutamine that is released from the lungs can be accounted for by the uptake of precursor nitrogen from the circulation in the form of ammonia and glutamate[11]. Although there is a smaller difference in the concentration of glutamine across the vasculature of the lungs than that of the limbs, the lungs have a higher blood flow and release a similar amount of glutamine into the circulation[12]. There is also a far lesser effect in the opposite direction; endothelial cells and type II alveolar cells consume glutamine and contain glutaminase.

Liver. The liver plays a central role in glutamine homoeostasis because it can either generate or consume glutamine. The periportal region contains glutaminase and is the site for urea biosynthesis. The hepatocytes in this region contain nuclear-encoded enzymes for the urea cycle, such as carbamoyl phosphate synthetase 1 and ornithine transcarbamoylase, within their mitochondrial matrix. Glutamine synthetase is present in specialized cells around the hepatic venous outflow that act as scavengers for ammonia[13]. This is a useful arrangement for mopping up ammonia from both the systemic and portal circulations. The latter is particularly important because, as discussed below, the gut generates ammonia.

Immune system. Lymphocytes require glutamine in order to proliferate in response to an antigenic challenge. Macrophages may consume glutamine as a source of energy and as a precursor for nucleotides. Souba and co-workers[12] have stressed that the immunodeficiency that characterizes critical illness may have a component that can be reversed by glutamine therapy.

Gut. The gut consumes large amounts of glutamine[14]. The small bowel epithelium can take up glutamine from either the lumen of the bowel (postprandial) or the bloodstream via its basolateral surface (postabsorptive). The normal first-pass extraction rate for glutamine in the gut is about 30 per cent and enterocytes have a greater than usual requirement for glutamine during the adaptive response to intestinal resection[2].

Kidney. The kidneys exhibit a net glutamine uptake in the postabsorptive state, but renal glutamine consumption becomes appreciable only during acidosis, when additional circulating glutamine is needed to support renal ammoniagenesis[15,16]. In acidosis, cells lining the initial part of the proximal convoluted tubule ensure that there is an asymmetrical release of end-products, i.e. bicarbonate into the renal vein and ammonium into the urine.

Regulation of glutamine metabolism

Besides the role played by the liver, the interorgan flow of glutamine is influenced by factors that regulate the activity of key enzymes and transport mechanisms[17]. Such factors include hormones, cytokines and endotoxins. In experimental models of physiological stress, dexamethasone mediates glutamine release from skeletal muscle, immunocytes and the lungs[18–21]. The effect of dexamethasone is due, at least in part, to an increase in the activity of glutamine synthetase in these tissues. In contrast, the increase in intestinal utilization of glutamine in response to dexamethasone is associated with an increase in the specific activity of intestinal glutaminase. Presumably the extra glutamine consumed by the gut is used to support energy requirements, glutathione production and nucleotide biosynthesis in the rapidly renewing cell population. The glutamine depletion that develops in skeletal muscle during endotoxaemia is caused by an accelerated release of glutamine from skeletal muscle, rather than by an increase in intracellular degradation or a fall in synthesis.

Growth hormone administered after surgery has beneficial effects on nitrogen metabolism as evidenced by an unchanged capacity for protein synthesis in skeletal muscle, preserved levels of muscle free glutamine and improvement in the whole-body nitrogen balance[22]. When given with parenteral nutrition after gastrointestinal surgery, growth hormone abolishes the loss of glutamine, 3-methylhistidine and total amino acid nitrogen from forearm tissue[23]. The effects of growth hormone on skeletal muscle protein and amino acid metabolism may explain the postoperative nitrogen-sparing effect attributed to growth hormone.

Austgen *et al.*[21,24] reported that the alterations in glutamine metabolism observed within the gut during sepsis can be reproduced by a single dose of interleukin 1. Furthermore, Parry-Billings *et al.*[25] found that the plasma glutamine level declined rapidly after major surgery and remained markedly below preoperative levels until at least 7 days after operation. This response paralleled the circulating levels of interleukin 6, but not those of interleukin 2, tumour necrosis factor, or interferon γ.

Glutamine as a specific substrate

In 1955, Eagle[26] investigated the nutritional requirements of tissue cultures and noted that the requirement for glutamine was much greater than that for any other amino acid. He also found that the selective omission of glutamine from tissue cultures leads to cell death. The rate of glutamine utilization by macrophages and lymphocytes is prodigious. In terms of energy, in the rat it is equivalent to about 25 per cent of the rate of glucose utilization by maximally working perfused heart[27]. In the enterocyte, the complete oxidation of 1 mol glutamine via the tricarboxylic lipid cycle yields 30 mol adenosine 5'-triphosphate (ATP), whereas glucose is metabolized only as far as pyruvate to produce a net yield of 2 mol ATP.

A high rate of glutamine uptake, but only partial oxidation, is characteristic of rapidly dividing cells, such as enterocytes, immunocytes, macrophages and fibroblasts. This situation provides ideal conditions for the synthesis of key molecules, such as glutathione and nucleotides[28], as well as the generation of energy (glutamine oxsynthesis). The teleological argument is that glutamine must be used at a high rate by these cells, even when they are quiescent, to allow for a rapid response to a challenge. The observation by Inoue *et al.*[29] that glutamine transport is not downregulated after bowel rest may further emphasize the importance of glutamine in the catabolic state.

The main pathways of glutamine metabolism are outlined in *Fig. 2*. Glutamine can be metabolized through glutamate semialdehyde in the jejunum to form proline, ornithine and citrulline; more than 25 per cent of

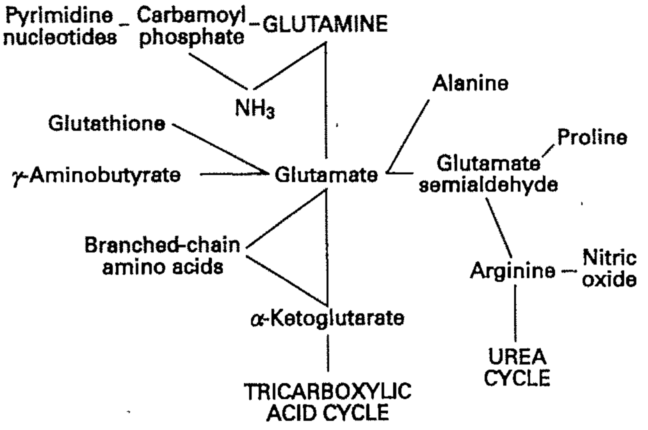

Fig. 2 Main pathways of glutamine metabolism

glutamine metabolized in the gut is released as citrulline[30]. Citrulline is converted to arginine, a key substrate for the synthesis of nitric oxide and lymphocyte immune responses[31]. Other protein end-products of glutamine metabolism are collagen via hydroxyproline, γ-aminobutyric acid and glutathione[32].

Glutamine is a conditionally essential nutrient

In 1938, Rose[33] reported that glutamine was a non-essential amino acid because it could be readily synthesized *de novo* within many tissues. However, in some conditions, such as extreme physical exertion, trauma and sepsis, the demand for glutamine may exceed the body's capacity to synthesize it. During such periods of catabolic stress the intracellular concentration of glutamine may decline by more than 50 per cent and the plasma level may fall by up to 30 per cent[2,8]. This has led to the reclassification of glutamine as a conditionally essential nutrient[34]. Branched-chain amino acids (isoleucine, leucine and valine) can be metabolized to glutamine in skeletal muscle. Branched-chain amino acid aminotransferase catalyses the transamination of branched-chain amino acids to yield glutamine via glutamate[35]. Hence, it has been speculated that infusions of branched-chain amino acids might be able to liberate glutamine from the free amino acid pool in skeletal muscle for consumption by the gut[36,37].

The ability to utilize specific nutrients varies along the length of the gut[38]. It makes good biological sense that the intestine should not be reliant on glucose, because it needs to function well after periods of starvation[39]. In this situation enterocytes use ketone bodies as a fuel[40]. Roediger[41] has stressed the metabolic importance of ketone bodies derived from short-chain fatty acids as intraluminal nutrients for the distal bowel. Indeed, Chapman *et al.*[42] have demonstrated that ketone bodies are the preferred fuels of large bowel mucosa, followed by glutamine and then glucose.

It is of interest that glutamine deprivation can be induced by injecting glutaminase. Baskerville and colleagues[43] gave various doses of glutaminase parenterally to Rhesus monkeys, marmosets, rabbits and mice. The enzyme induced diarrhoea and dysentery and, at all but the lowest doses, caused death within 10 days. Pathological lesions produced were hepatic lipidosis and glycogen accumulation, and, in the primates, acute necrotizing colitis.

Gut atrophy

Animals sustained on parenteral nutrients develop atrophy of the gut. In 1987, Hwang *et al.*[44] reported that the infusion of glutamine-enriched solutions of parenteral nutrients resulted in an increase in the mucosal weight and DNA content of the small bowel in rats. It is now appreciated that there is a dose–response relationship between the concentration of glutamine infused and the extent of atrophy in the small bowel (but not in the large bowel)[17]. Although such findings are useful for formulating clinical hypotheses, there are interspecies variations in the intestinal response to starvation. For example, rats develop an obvious atrophic gut after several days of starvation, whereas healthy human volunteers sustained on parenteral nutrients for up to 14 days develop only a mild decrease in villus height[45].

A further issue is whether the amelioration of gut atrophy by the provision of glutamine is associated with any local functional advantage. Laboratory studies have demonstrated that the provision of glutamine enhances a wide range of processes relating to the alimentary tract during periods of catabolic stress, e.g. maturation of the intestine during growth, adaptive hyperplasia after resectional surgery, healing of chemically induced enterocolitis, better preservation of intestinal segments used in small bowel transplantation and prevention of atrophy of the exocrine pancreas[46–51]. There is no substantive evidence that glutamine can enhance wound or anastomotic healing[52,53].

Glutamine and the gut barrier

Besides acting as an organ of digestion and absorption, the gut must provide a barrier against invading pathogens and noxious molecules. This barrier is dynamic in nature and extends to the hepatic reticuloendothelial cells picketing the main portasystemic junction (*Table 2*). It is important to appreciate that the gut barrier is a layered process: even the secretory immunoglobulin effector activity is a three-tiered mechanism[54]. Increased intestinal permeability and translocation of bacteria have been observed in a large number of controlled animal experiments investigating situations of relevance to clinicians (*Table 3*).

Intestinal permeability

The epithelium lining the gut selectively prevents the passage of water-soluble molecules[55,56]. Changes in intestinal permeability can be assessed by measuring the passage of inert molecules such as mannitol, lactulose, dextran and polyethylene glycol. In the absence of breaches in the epithelium, it is assumed that changes in permeability reflect alterations in the paracellular junctional complex, a dynamic gate that opens and closes in response to a variety of influences. For example, amino acid transport systems on the apical surface of enterocytes may be coupled via cytoskeletal elements to contractile actomyosin of tight junctions[17]. The size of the junctional complex allows passage of molecules such as small antigens derived from the diet or bacteria, but not bacteria or endotoxins.

Table 2 Layered components of the gut barrier

- Local innate immune mechanisms
  - Gastric acidity
  - Flushing effect of gut motility
  - Intraluminal digestive events
  - Unstirred mucous layer in the glycocalyx
  - Tight intercellular junctions between enterocytes
  - Rapid turnover of enterocytes along the cryptovillus axis
- Adaptable immune mechanisms (gut-associated lymphoid tissue)
  - Antigen sampling
  - T cell responses
  - Production of secretory immunoglobulins
- Systemic mechanisms
  - Refinement of adaptable immune mechanisms
  - Macrophage activity

Tabe 3 Animal models associated with the translocation of bacteria across the wall of the gut

- Splanchnic ischaemia
- Thermal injury
- Sepsis
- Trauma
- Parenteral nutrition
- Bowel obstruction
- Antimicrobial therapy
- Obstructive jaundice
- Cytotoxic therapy

Intestinal permeability appears to be an accurate global marker of illness in critically ill patients[57–59] and Cummins *et al.*[60] have demonstrated that the upper gut atrophy resulting from prolonged enteral feeding is associated with altered intestinal permeability. Animal studies have shown that parenteral or enteral administration of glutamine can prevent inappropriate increases in the permeability of the gut[61,62].

Bacterial translocation

The phenomenon of bacteria crossing the gut mucosal barrier and invading extraintestinal tissue has been termed bacterial translocation[63,64]. In 1969, Krause and co-workers[65] reported that the swallowing of a solution containing *Candida albicans* resulted in a transient toxic reaction with recovery of yeast from both blood and urine within a matter of hours. It has been suggested that, in critically ill patients, microbes and endotoxins can pass across the wall of the gut and create a 'gut origin septic state'. This has been proposed as an important underlying event in patients with septic multiple organ failure syndrome[66]. In this way, the leakage of microbes and their products into the portal blood of critically ill patients may designate the gut as the 'undrained abscess' of septic multiple organ failure syndrome[67].

Although there is considerable experimental evidence to link a failure of the gut barrier with septic multiple organ failure syndrome, the strength and clinical significance of this relationship have yet to be established[68]. Nevertheless, the concept is compelling and it does explain the often observed phenomenon of stressed patients becoming septic in the absence of a defined focus of infection. The pathogens that occur most frequently in patients with septic multiple organ failure syndrome are the same organisms that have been observed to translocate across the wall of the intact gut, i.e. *C. albicans, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa* and *Enterococcus.*

Although Alverdy[69] has shown that glutamine enhances the function of the mucosal immune system in the gut, there is controversy about the ability of glutamine to prevent bacterial translocation in various animal models[70–73]. The issue is complicated by the fact that sepsis adversely influences both the metabolism and function of the gut mucosa[74–77].

Clinical studies

Most naturally occurring food proteins contain 4–8 per cent of their amino acid residues as glutamine[2] and so the daily consumption of glutamine is usually less than 10 g. However, it may be necessary to consume between 20 and 40 glutamine per day to maintain homoeostasis after a severe catabolic insult[1]. Glutamine cannot be marketed in liquid products that have a long shelf-life because it decomposes to form pyroglutamate and ammonia, but it is stable in nutrient solutions for at least 22 days when stored at 4°C[78]. It is also possible to administer glutamine precursors, such as α-ketoglutarate, and dipeptides, such as alanine–glutamine[79,80]. In the human intestine the predominant mechanism for assimilation of glutamine dipeptides is absorption as intact dipeptides rather than hydrolysis[81].

Enteral nutrition

As yet, there has been no substantive clinical trial evaluating the worth of enteral solutions containing glutamine. Nevertheless, solutions of such enteral nutrients are available commercially in many countries. The lack of clinical trials reflects problems in the accrual of adequate numbers of patients, methodological issues related to the assessment of critically ill patients, and a lack of research funds. The last is aggravated by the fact that nutrients are classified as foods rather than drugs and are sold as high-volume low-profit items.

The provision of enteral glutamine to healthy volunteers does not appear to be associated with any adverse metabolic events[82]. However, Mebane[83] described two people who developed symptoms of mania and hypomania after self-medication with up to 4 g glutamine per day as tablets purchased from 'health food' stores. In this context, glutamine is a precursor of γ-aminobutyric acid, which may act as a neurotransmitter.

Parenteral nutrition

Pironi *et al.*[84] have provided additional evidence that gut atrophy occurs in patients receiving parenteral nutrition. They performed a longitudinal study of the morphological and cytoproliferative patterns of the duodenal mucosa in two patients after resectional surgery. It was concluded that hypoplasia of the duodenal mucosa develops after long-term parenteral nutrition. Mucosal recovery occurs by means of increased cell proliferation after oral refeeding and the extent of the gut resection determines the development of relative hyperplasia.

A number of diverse, but interesting, publications have addressed issues relevant to the parenteral use of glutamine for surgical patients (*Table 4*). Overall, there is

Table 4 Clinical investigations of parenteral glutamine

Reference	Findings
Stehle *et al.*[85]	Improvement in nitrogen balance and conservation of the intramuscular glutamine concentration in patients undergoing colorectal surgery
Wernerman *et al*[86]	Administration of glutamine and ornithine-α-ketoglutarate reduced the loss of muscle glutamine from 40 to 25 per cent after elective abdominal surgery
Steininger *et al*[87]	Glutamine-containing peptides enhanced intramuscular glutamine concentration in patients with acute pancreatitis
Hammerqvist *et al.*[88]	Less nitrogen loss and sparing of intramuscular polyribosomes in patients undergoing elective abdominal surgery
Fong *et al.*[89]	In patients receiving conventional parenteral nutrition, enterectomy was associated with a marked decrease in the efflux of glutamine from skeletal muscle; it was suggested that the gastrointestinal tract provides a feedback signal to peripheral tissues to maintain glutamine mobilization
Ziegler *et al.*[90]	Dose–response studies demonstrated good tolerance without untoward clinical or biochemical effects
Darmaun *et al*[91]	Rate of whole-body glutamine utilization was reduced by 20 per cent after extensive small bowel resection
McAnena *et al.*[14]	Catheters were placed in the portal veins of patients undergoing laparotomy for major trauma; it was confirmed that selective uptake of glutamine does occur in the gut
van der Hulst *et al.*[80]	In healthy volunteers, glutamine-supplemented parenteral nutrition diminished the extent of intestinal permeability and preserved the morphology of the intestine
O'Riordain *et al.*[92]	T cell DNA synthesis was increased compared with both preoperative values and a group receiving conventional parenteral nutrients
Ogle *et al.*[93]	Glutamine enhanced the bactericidal function of neutrophils from patients with burns; this was not associated with an effect on the expression of C3b receptors
Hornsby-Lewis *et al.*[78]	Seven patients receiving home nutritional support received glutamine supplements for 4 weeks. Two patients ceased therapy because of a transient increase in liver enzyme levels
Petersson *et al*[94,95]	Intramuscular glutamine concentration was still about 20 per cent below normal 30 days after cholecystectomy. Although the dipeptide glycyl-glutamine maintained intramuscular glutamine levels after surgery, the glutamine concentration in muscle dropped when glutamine supplements were withdrawn despite a normal oral intake
Petersson *et al.*[96]	Glutamine makes no difference to subjective feelings of fatigue after open cholecystectomy
Tremel *et al.*[97]	Glutamine dipeptides in physiological doses can compensate for the increased intestinal requirements for metabolic fuel during critical illness

strong evidence that glutamine enhances nutritional status by promoting a positive nitrogen balance and conserving skeletal muscle. There is also sufficient evidence about glutamine and the gut barrier to warrant more detailed clinical studies aimed at defining the possible clinical advantages of providing glutamine supplements to surgical patients. Several clinical trials have addressed the use of parenteral glutamine in patients undergoing bone marrow transplantation. Before these studies it had been established that high nitrogen regimens can reduce the loss of lean body mass in such patients[98]. Ziegler *et al.*[99] reported that patients receiving glutamine had fewer nosocomial infections and went home sooner. Schloerb and Amare[100] agreed with these findings, but failed to identify any other specific benefit. Data from a study by Scheltinga *et al.*[101], together with the results of laboratory studies, suggest that glutamine may prevent the extravasation of water into the extracellular compartment of critically ill patients. Young and co-workers[102] performed a trial evaluating mood changes, and concluded that patients receiving glutamine had better retention of vigour and felt less angry at time of completion of the study.

The construction of reliable clinical studies to evaluate glutamine therapy in surgical patients will be a difficult task. The important endpoints relate to infection, organ failure, death and prolonged stay in hospital, but these are influenced by many other factors. The benefits accrued by administering glutamine will influence but one link in a chain of 'stacked intolerance'. Trying to overcome some of these problems by studying large numbers of patients will pose a challenge in terms of logistics and finance. There is already a lack of comprehensive clinical trials evaluating more general aspects of nutritional support techniques in surgical patients.

Conclusion

The commercial availability of stable forms of glutamine should eventually result in a new generation of solutions of nutrients. However, the degree to which such a change would benefit surgical patients is difficult to assess. It would certainly enhance aspects of nitrogen metabolism, but it has yet to be demonstrated that this would translate into clinical advantages, such as better wound healing or speedier rehabilitation. The effects of glutamine on the immune system and the gut barrier are intriguing, and are relevant to efforts aimed at preventing septic multiple organ failure syndrome.

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Editor's announcement

Illustrations in colour

The Journal does not contain many illustrations in colour at present, probably because authors are usually requested to make a contribution towards the cost of colour reproduction. This cost is substantial, amounting to approximately £500 per figure at current rates. In association with the publishers, Blackwell Science Ltd, The British Journal of Surgery Society is keen to increase the number of colour illustrations in the Journal. The use of colour is particularly appropriate for operative photographs (whether open operation or laparoscopy), resection specimens and especially photomicrographs. To encourage the submission of suitable illustrations in colour, authors' charges will be waived. Three high-quality prints of each figure should be submitted.

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Review

Role of cytokines and growth factors in promoting the local recurrence of breast cancer

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The pathogenesis of local recurrence in breast cancer is not well understood. Breast-conserving surgery is particularly prone to local recurrence as it leaves behind breast tissue that may harbour occult cancer, and lends itself to enhanced intraoperative shedding of cancer cells due to narrower resection margins and transection of lymphatic channels. A review of clinical breast cancer studies as well as experimental research strongly suggests that these persisting cancerous cells are unlikely to develop into clinically evident disease if their environment remains unstimulated. However, an inordinately high local recurrence rate occurs at the surgical scar, and such recurrence must be triggered by the release of growth factors and cytokines into the healing wound. These factors can stimulate any available cancer cells which express the proper growth factor receptors. Perioperative strategies to neutralize this tumour cell–growth factor interaction should maximize local control.

The pathogenesis of local recurrence in breast cancer remains a perplexing problem in surgical oncology. The dominant paradigm is that local relapse after primary tumour removal is due to growth of cancer cells left behind at operation because of inadequate surgical technique[1]. A corollary is that, if surgery completely removes all cancerous tissue in the breast, then local recurrence cannot occur[2]. This is the basis for the Halstedian principle[1] that stressed that the extent and nuances of the mastectomy were the critical factors in determining local recurrence: 'The suspected tissues should be removed in one piece, (1) lest the wound become infected by the division of tissue invaded by the disease or by lymphatic vessels containing cancer cells, and (2) because shreds or pieces of cancerous tissue might readily be overlooked in a piecemeal extirpation'. This philosophy has served as a guiding principle of surgical oncology and has dictated the utilization of radical surgery to maximize local control and optimize cure.

Partly out of frustration with the inability of radical surgery to cure more patients, a second paradigm was formulated. Fisher proposed that the ultimate prognosis in breast cancer may be already predetermined by the extent of systemic micrometastasis present at diagnosis[3], such that variations in locoregional treatment and control were unlikely to affect survival. The importance and purpose of surgery was called into question. Breast-sparing procedures were initiated that compromised Halstedian principles by creating narrow resection margins around the tumour and by transecting draining lymphatic channels rather than *en bloc* removal of lymph nodes.

Today, with an even greater percentage of early cancers being diagnosed, micrometastasis may not have occurred before surgery. It is likely that a greater proportion of distant metastasis may now actually be the result of intraoperative dissemination of cancer cells. Thus the dynamics of the physiological responses during the intraoperative period assume greater importance. One of the critical events occurring as a result of injury and inflammation is the release of cytokines and growth factors. This response, it is hypothesized, may be capable of stimulating residual established cancers[4,5] or enhancing the survival of freed tumour cells disseminated at the time of surgery.

In this review, the basis for this hypothesis is examined as follows:

1. Wider resection around a tumour results in only limited improvement in local control, implying that persistence of local disease is not the major cause of local recurrence.
2. Tumour cells disseminated at surgery account for a significant number of local recurrences and possibly distant metastases.
3. Growth factors and cytokines from the healing wound can stimulate cancer cells that are released during operation as well as residual, potentially dormant, cancer cells that reside adjacent to the surgically injured site.

It is postulated that a new unified theory taking into account these data will suggest a new paradigm in breast cancer management: the contribution of tissue growth factors to local recurrence.

Extent of resection in determining the rate of local recurrence

All local recurrences of cancer theoretically may be related to incomplete eradication of disease and so may be preventable by a more extensive procedure However, despite varying degrees of surgery, the local recurrence rate of breast cancer has remained relatively constant over the years; it is more closely related to the characteristics of a given tumour and to the effectiveness of adjuvant treatments[6].

The failure of more radical resection to lessen chest wall recurrence is highlighted by the treatment of the mastectomy skin flaps[7]. The majority of local recurrences after mastectomy occur in the skin and immediate

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subcutaneous tissues of the mastectomy flaps adjacent to the surgical scar[8]. Attempts to prevent this recurrence led some surgeons to remove a very wide area of skin in continuity with the breast. Conway and Newmann[9], in 1949, proposed that recurrence rates in the breast did not decrease proportionately with the extent of mastectomy. They retrospectively evaluated skin grafting performed in conjunction with radical mastectomy. After controlling for tumour size and axillary node metastasis, a 21 per cent incidence of local recurrence was found for operations utilizing skin grafting, compared with only 9 per cent when a smaller ellipse of skin was removed allowing for primary closure of the mastectomy flaps. This failure to minimize skin recurrence with wider removal of the skin has been confirmed by others[10]. Another surgical technique to prevent recurrence in the mastectomy flaps was the formation of very thin skin flaps. It was believed that skin recurrence was a manifestation of subcutaneous spread of tumour cells which could be prevented with extensive subcutaneous dissection of the skin flaps. However, Crile[11] demonstrated that a low rate of local recurrence was achieved by preserving minimally injured, thick mastectomy skin flaps that had an adequate blood supply.

Despite varying techniques of radical surgery, the local recurrence rate has remained relatively constant over the years. It appears unlikely that residual disease missed at a more radical operation could account for chest wall recurrence. This is particularly apparent if the site where the cancer is likely to recur has been removed by more radical surgery, and still has no effect on the rate of local recurrence. Furthermore, recent studies on breast conservation have demonstrated that lumpectomy has a rate of chest wall recurrence equivalent to that of mastectomy. In this context, chest wall recurrence after breast conservation is defined as in-breast recurrence that cannot be resected or that recurs locally after salvage mastectomy. At the 10-year follow-up of the National Surgical Adjuvant Breast and Bowel Project (NSABP) study[12], mastectomy carried a rate of chest wall recurrence of 9·8 per cent, while lumpectomy without radiation therapy was associated with a chest wall recurrence rate of 8·2 per cent. The low rate of chest wall recurrence associated with lumpectomy and radiotherapy (2·2 per cent) is consistent with reports that the addition of radiation therapy results in a 35–80 per cent decrease in the local recurrence rate[13].

In contrast to chest wall recurrence following total mastectomy, in-breast local recurrence is generally attributable to residual microscopic foci of cancer persisting in the breast after breast-conserving surgery. This is a factor not applicable in total mastectomy where all breast tissue has already been removed. Most histological studies on mastectomy specimens describe a 30 per cent or greater incidence of other microscopic foci of cancer at a discrete distance from the index tumour[14]. The majority of these foci are ductal carcinoma *in situ* (DCIS)[14]. Neoplastic foci distinct from the index tumour can be classified as multifocal or multicentric. Multifocal lesions are defined as foci of cancer in the same quadrant as the primary cancer which may represent extension of, or metastasis from, the primary tumour. Multicentricity is defined as foci of cancer in quadrants of the breast different than that of the primary tumour, probably representing independent neoplastic events. Multicentric foci are also seen in the contralateral breast as frequently as in the remaining three quadrants of the ipsilateral breast away from the index tumour[15]. However, occult foci of microscopic cancer do not necessarily result in clinical disease. In autopsies of women with a previous diagnosis of breast cancer, Alpers and Wellings[16] found DCIS in 48 per cent of contralateral breasts, even though only 12·5 per cent of all patients with breast cancer develop contralateral breast cancer after 20 years of follow-up. Furthermore, autopsy studies in women without a history of breast cancer reveal an appreciable incidence of occult breast neoplasms. In women over 70 years of age the incidence of occult DCIS is 19 times greater than the prevalence of clinical breast cancer at that age[15]. Even in low-risk women 20–54 years old, occult breast cancer was detected at autopsy in 20 per cent, with 90 per cent of these being non-invasive forms[17]. Additionally, it is rare to find clinically evident multifocal breast cancer even in women with advanced breast carcinoma. These data led Fisher[3] to question whether every clinically occult lesion in the breast needs to be treated, and to consider lumpectomy without radiotherapy as adequate local therapy for breast cancer.

Previous studies demonstrating microscopic foci away from the primary tumour were from older series of consecutive mastectomies, including cases that by multiple criteria would not have been eligible for breast conservation by today's standards. Holland *et al.*[18], utilizing the much smaller cancers than are seen today, analysed mastectomy specimens utilizing Egan's technique of cutting thin sections from the entire breast and performing mammography on each section to help identify suspicious areas for further microscopic study. They demonstrated that there was a great likelihood of residual cancer within the immediate area of the biopsy site. The frequency of residual cancer decreased as the distance from the primary index tumour increased. Removing 2 cm of extra tissue around an index tumour would have left residual cancer in 42 per cent of the breasts. With a margin of 4 cm, residual tumour would have been in 10 per cent of the breasts. This 4-cm margin is considered equivalent to quadrantectomy for small cancers of the breast. The incidence of residual microscopic cancer after quadrantectomy is probably no different from the incidence of occult tumours seen in the contralateral breast[19]. However, overt clinically detectable cancer develops much more frequently in the ipsilateral breast if no radiation therapy is given[20].

If the residual cancer theory of Holland *et al.*[18] is clinically relevant, recurrence rates in the breast should decrease proportionately with the extent of partial mastectomy. There is only one randomized clinical trial (Milan II)[21] that has evaluated in-breast recurrence with respect to the extent of surgery (quadrantectomy *versus* lumpectomy). However, both groups received postoperative radiation, which can significantly alter the destiny of any residual cancer. To evaluate the incidence of local recurrence, different extents of breast-conserving surgery without the administration of postoperative radiotherapy which might delay or prevent its occurrence need to be analysed. Analysis of the four large randomized series that have evaluated breast-conserving surgery without radiotherapy gives insight into the effects of different surgical procedures (lumpectomy, sector resection and quadrantectomy) on local recurrence (*Table 1*).

Local recurrence after lumpectomy

In the NSABP B-06 trial[22,23] lumpectomy required

Table 1 Randomized trials evaluating radiation in breast-conserving surgery

Trial	Procedure	Selection characteristics	Length of follow-up	Local recurrence*	
				No radiation	Radiation
NSABP[12,22,23]	Lumpectomy	Tumour diameter ≤4 cm	39 months	93 of 56[illegible] (16·5)	25 of 566 (4·4)
		Positive nodes (35 per cent)	81 months	175 of 57[illegible] (30·6)	39 of 569 (6·9)
		Negative histological margins	10 years	206 of 57[illegible] (36·0)	61 of 568 (10·7)
Princess Margaret[24,25]	Lumpectomy	Tumour diameter ≤4 cm	43 months	108 of 42[illegible] (25·7)	23 of 416 (5·5)
		Negative nodes	5 years	— (30)	— (8)
		Negative histological margins			
Milan[20]	Quadrantectomy	Tumour diameter ≤2·5 cm	39 months	28 of 27[illegible] (10·3)	1 of 294 (0·3)
		Positive nodes (30 per cent)			
		Negative surgical margins			
Swedish[26,27]	Sector resection	Tumour diameter ≤2·0 cm	3 years	7·6 per cent	2 of 182 (2·9)
		Negative nodes	5 years	18·4 per cent	3 of 181 (2·3)
		Negative histological margins			
		No multifocal sites at >2 cm			
		No contamination			

*Values in parentheses are percentages

microscopically negative surgical margins; however, the amount of tissue removed around the tumour was not specified. Wide margins were not required and adequate small margins were implied, emphasizing the cosmetic result. Most axillary dissections were performed through separate incisions, not *en bloc* with the primary tumour. The in-breast local failure rate was 40·9 per cent at 10 years for lumpectomy alone, compared with 12·4 per cent for lumpectomy with radiotherapy[12]. This high rate of in-breast local recurrence after lumpectomy alone is not surprising since it corresponds with the data of Holland and co-workers[18] concerning the incidence of residual cancer more than 2 cm from the index tumour. Furthermore, after 8·5 years of follow-up, all in-breast recurrences after lumpectomy with or without radiation were at the surgical site of the excised tumour and not in a different quadrant of the breast[28]. This finding of local recurrence solely in the area of the surgical extirpation markedly minimizes the clinical and biological significance of multicentricity, i.e. microscopic cancer foci away from the index tumour quadrant do not appear to lead to clinically evident malignancies. The NSABP investigators[29] concluded that most, if not all, in-breast failure represented residual cancers resulting from either inadequate resection margins or from growth of multifocal sites within the same quadrant. There appeared to be no biological consequences for multicentric foci of tumour in other quadrants.

Other lumpectomy series have also shown the predominance of local recurrence in the same quadrant as the original tumour site[24]. After the first 10 years of follow-up, 70–80 per cent of all in-breast recurrences after surgery and radiation occurred in the same quadrant as the original tumour[30]. Less frequently, and more often as a late effect, tumour formed in other quadrants distant from the primary lesion. This occurred in 1 per cent at 5 years and in 3–4 per cent at 10 years in Kurtz's study[31]. Thus, the histological data of Holland *et al.*, as well as the recurrence data with lumpectomy, suggest the prime importance of residual cancer at the surgical site and the minimal importance of cancer at sites outside of the index quadrant. These observations further suggest that quadrantectomy may be the ideal operation for removal of the index cancer, since the remaining three quadrants should have risks similar to those of the contralateral breast, where radiation therapy is unnecessary.

Local recurrence after more radical (quadrant or sector) resection

In the Milan trial[21], quadrantectomy was used for cancers 2·5 cm or less in diameter. The surgical procedure[32] consisted of the radical removal of the entire breast quadrant containing the tumour. The overlying skin and corresponding area of pectoralis major fascia were removed. Axillary nodes were removed *en bloc* when feasible. After 39 months of follow-up, there was a 10·3 per cent in-breast recurrence in the quadrantectomy-alone group with 9 per cent at the surgical site[20] (*Table 1*). At such a short follow-up the recurrence rate appears too high based on the data of Holland *et al.*, especially since the tumours were smaller than those in the NSABP study.

In the Swedish trial[33], wide resection margins (sector resection) with and without radiation therapy were performed for tumours 2·0 cm or less in diameter. Sector resection is similar to quadrantectomy except that it does not always involve a 90° angle segment. Its extent depends on the size and location of the tumour and is analogous to 'radical' lumpectomy[33]. Besides the smaller tumour size, the selection criteria were quite restrictive[26] (*Table 1*). Patients were excluded if either the tumour was transected during the surgery or the specimen contained microscopic cancer cells more than 2·0 cm from the index tumour, even if the surgical margins were histologically negative. The effect was to select a favourable T_1N_0 subgroup, excluding patients at risk of residual microscopic foci of cancer or of cancer contamination of the surgical wound.

The life-table estimates of in-breast recurrence rate after 3 years were 2·9 per cent with radiation therapy and 7·6 per cent without radiation therapy. The authors concluded[26] that 'meticulous surgical technique may be an alternative to routine radiation therapy in selected cases'. However, in their more recent 5-year follow-up, the in-breast local recurrence rate was 2·3 per cent in the irradiated group and 18·4 per cent in the non-irradiated group[27] (*Table 1*). This 5-year in-breast recurrence after sector resection alone (18·4 per cent) is similar to the

NSABP life-table analysis at 5 years of 24 per cent, despite a more advanced tumour treated with the less surgically extensive lumpectomy[34]. This is even more remarkable considering the less stringent eligibility criteria in the NSABP trial. The investigators were puzzled by the high local recurrence rate and, without an explanation for the local failures, they faulted the surgeons[35].

This, lower than expected, benefit of the more radical partial mastectomy on in-breast recurrence detracts from the 'residual cancer theory' of local recurrence. Furthermore, it is a challenge to explain the peculiar tendency of tumours to recur directly in the surgical field, despite clear histological margins and no apparent contamination at the time of surgery.

Tumour cell dissemination during surgery

Surgical resection of breast cancer results in intraoperative dissemination of tumour cells even though the boundaries of the cancerous lesion are never violated. There can be dissemination systemically into the bloodstream. There can also be local shedding of tumour cells around the wound due to severed lymphatic and venous channels, opened interstitial tissue planes or transected breast ducts.

Tumour cells shed haematogenously

Several early studies demonstrated cancer cells in the circulating blood of patients with breast cancer. Roberts *et al.*[36] demonstrated that preoperative surgical scrubbing and intraoperative surgical manipulation increased the seeding of breast cancer cells into the blood. Turnbull in Bell[37] observed that blood from the mesenteric veins of patients with colonic cancer contained few, if any, tumour cells if the tumour was not manipulated during operation; however, after manipulation, the blood was showered with tumour cells in 30 per cent of cases. These early studies used unreliable techniques which resulted in a wide range (0–100 per cent) of cancer cell detection in the blood[38], causing some investigators to question the findings. More recent advances in molecular biology utilizing polymerase chain reaction (PCR), reverse transcriptase–PCR (RT–PCR) and monoclonal antibodies allow a more accurate means of identifying circulating cancer cells[39–42]. These studies have reaffirmed both the presence of circulating cancer cells in the blood and the haematogenous release of such cells during the surgical removal of tumour. The cells disseminated into the circulation can potentially give rise to distant metastases, or to local recurrence by returning to the surgical wound[43].

Animal studies have demonstrated frequent spontaneous haematogenous shedding of cancer cells, involving as many as 10 per cent of tumour cells undergoing division[44]. As the tumour grows, the number of cells shed into the circulation increases[45]. Furthermore, the greater the number of cancer cells introduced into the circulation at any one time, the greater the chance for tumour implantation and growth at a suitable site[46]. Trauma to the tumour affects cell detachment by increasing the spread of tumour cells along interstitial planes as well as systemically[47]. Manipulation of animal tumours simulating intraoperative conditions increases haematogenous dissemination[48] as well as increasing the incidence of distant metastasis[49].

Fortunately, the overwhelming majority of circulating tumour cells are rapidly destroyed in the bloodstream within 24 h[50]. It is estimated that between 0·01 and 0·1 per cent of these circulating tumour cells survive to proliferate into metastases[50,51]. Special criteria must be fulfilled for circulating tumour cells to survive and develop into secondary tumours. A given tumour phenotype generally metastasizes only to certain favoured sites, despite lodging in the microvasculature of many different sites[52]. Radinsky and Fidler[53] attributed this phenomenon of site selectivity to the growth factor microenvironment of the favoured target organ, i.e. if the right growth factors are present and active, and the tumour has the appropriate growth factor receptors, then implantation and growth is possible.

Tumour cells shed in the surgical wound

Despite the correct objectives of the Halstedian approach to the surgical cure of breast cancer, there is no operation that totally avoids local intraoperative shedding of tumour cells. Partial mastectomy is even more likely to disseminate cancer cells locally. Clinically, local spillage of cancer cells is believed to increase local recurrence. This is demonstrated in studies showing an increased local recurrence rate with intraoperative perforation of the specimen[54–56]. In other clinical situations without obvious contamination, cancer cells have been found in the washings of the operative wound[57] and in analysis of postoperative drainage fluid[58]. A recent study from Germany[59] analysed blood shed from the surgical field during oncological surgery. Some 57 (93 per cent) of 61 patients demonstrated free cancer cells in the surgical field despite the usual oncological surgical measures taken to minimize such spillage. During radical prostatectomy procedures, investigators from the authors' institution detected prostatic cells using RT–PCR in 20 of 22 operative field blood samples and in ten of 22 intraoperative peripheral venous blood samples (K. Kaul, personal communication).

Surgical wounding, cancer cells and growth factors

Growth factors are specialized polypeptides that coordinate and regulate cellular activity. These growth factors are normally secreted at only basal levels to maintain homoeostasis, but the levels vary with the hormonal environment and age of the individual. The growth factor levels markedly increase in response to injury, carcinogens or the mere presence of neoplastic cells. They are responsible for the extremely rapid cell division present in embryogenesis, cancer and early wound healing[60,61]. Growth factors are also the mediators by which oestrogen and progesterone stimulate both normal and neoplastic mammary tissue[62,63].

Surgical injury triggers an orderly sequence of events which is orchestrated via the local production of growth factors and other cytokines. Platelets initiate this injury-induced growth factor response, and these cytokines attract inflammatory cells, fibroblasts, endothelial cells and other cells involved in wound healing to the injured site. These migrated cells can then be stimulated into cell proliferation and into producing other growth factors and cytokines. Thus the types and concentrations of cytokines, as well as the types of cells in a wound, are in a dynamic state during wound healing[64,65]. The wound-healing process is dependent on one type of cell producing growth factors that act on another type of cell (paracrine mechanism). Cancer cells respond to these same chemoattractants, express similar receptors and respond to similar growth factors as do the body's natural inflammatory and mesenchymal cells when responding to tissue injury[66,67]. It would be surprising if neoplasms did not utilize these paracrine growth factor pathways of wound healing to establish local tumour recurrence.

This is in contrast to established cancerous cell populations, which can achieve a state in which they autoproduce the growth factors essential for their own proliferation, the so-called autocrine mechanism[61]. This effect of tumour cells allows them (after they have reached a critical mass number of cells) to become more independent of the need for growth factors from the non-neoplastic host cells. However, this is probably not the case for single, or small clusters of, tumour cells. It is postulated that host-derived growth factors would be necessary for tumours to 'take' and grow from isolated tumour cells until that critical mass is attained[68,69]. A dependence of certain types and concentrations of growth factors explains why only specific sites and set times act as favourable environments for cancer cell growth[70]. This explains why haematogenously shed cancer cells tend to grow only at favoured sites and why cancers tend to metastasize to preferred distant sites[53].

Furthermore, there is growing experimental evidence that a growth factor-stimulated microenvironment facilitates the survival of free, non-implanted, cancer cells which are left in an area of cancer extirpation or which are freely disseminated in the bloodstream. As early as 1914, Jones and Rous[71] noted that special circumstances were needed for intraperitoneally injected tumour cells to develop into a tumour: 'Reactive changes immediately around a point of injury come to the support and nourishment of the tumor cells'. Similarly, others have postulated that factors released by host cells into the inflammatory wound environment to promote wound healing also facilitate tumour growth[72,73]. Davies *et al.*[68] demonstrated that an intraperitoneal inoculum of more than 1000 murine mammary carcinoma cells was required to establish a 'metastatic' nidus. However, by inducing a macrophage-rich ascites plentiful in growth factors, as few as ten cells were adequate for tumour take. Likewise, Baker and colleagues[74] determined that the number of cancer cells necessary for tumour take after subcutaneous injection was significantly reduced by a factor of ten when cancer cells were injected into a surgical flank wound rather than into a non-wounded flank. This decreased threshold for tumour take was reproducible in three different tumours. Murphy *et al.*[52] have also demonstrated an enhanced efficiency of tumour take with haematogenous injected tumour cells after a surgically induced injury. The probability of intra-arterially injected sarcoma cells colonizing the muscle of a laparotomy wound was 1000 times more likely than if the muscle was not traumatized. Using a murine mammary adenocarcinoma model, Murthy and Scanlon[75] demonstrated that tumour cells injected intravenously never implant in the spleen. However, after injury to the lower pole of the spleen, these cancer cells implant exactly at the site of the surgical wound in the spleen in 76 per cent of cases. This predilection for tumour cells to implant at the site of injury has also been demonstrated with surgical trauma to liver, bone, colon and kidney[75-77]. Tumour take was dependent on the cancer cells being administered at the time of, or shortly after, the surgical injury, when the local area was considered to be rich in growth factors. As the wound aged, however, the surgical site became increasingly refractory to tumour implantation. When healing was complete, injected tumour cells had no affinity for the old surgical site[78]. Thus, contrary to previous beliefs that local recurrence can be a late manifestation of metastatic disease[10,79], the haematogenous return from a distant site to a healed scar is unlikely. Even local recurrence found in conjunction with widespread metastatic disease is likely to have arisen from the perioperative period rather than as a late phenomenon.

There is evidence that a growth factor-stimulated microenvironment affects growth of established residual tumour foci. Most clinically occult and microscopically *in situ* breast cancers remain dormant and do not progress to overt infiltrating lesions. However, surgical trauma may trigger these dormant cells to grow[80]. The proximity of the tumour cells to the site of injury appears to be an important factor since growth factors tend to act locally within the immediate vicinity of the injured site. This accounts for the activation of the microscopic breast cancer cells in the immediate area of the surgical scar and not in quadrants away from the surgical excision. Following non-curative resection of various tumours, there is an increase in the proliferative activity of the remaining tumour cells[81,82]. Simpson-Herren *et al.*[82] demonstrated that this increase in the rate of tumour cell proliferation occurs within 24 h of surgery and rapidly recedes over a few days. This enhancement of tumour proliferation is attributed to modulation of the growth factor environment[4,5]. Similarly, experimental evidence indicates that microscopic intrahepatic lesions[83,84], as well as established macroscopic liver metastases[85], can be growth stimulated by partial hepatectomy. These findings are analogous to the normal hepatocyte function after partial hepatectomy, which displays a marked cellular proliferation that peaks on the second or third postoperative day and returns to near preoperative levels by 1 week, when the original organ mass is regained[86]. It is postulated that the growth factors produced by the regenerating liver act as tumour-promoting agents. This is not surprising since *in vitro* studies of human breast cancer cell lines have demonstrated growth of otherwise dormant cancer cells when specific growth factors are added to the culture media[87], as well as inhibition of proliferating human breast cancer cell lines when anti-growth factor receptor antibodies are added to the growth medium[88].

Conclusion

Until these complex growth factor and cytokine responses are better understood and it is appreciated that even minimal trauma to cancer may result in local and systemic shedding of cells, surgical results will be less than optimal. Despite up-to-date adjuvant treatments, present results of total mastectomy for larger palpable cancers will still be associated with a poorer local recurrence rate than would otherwise be predicted by prognostic factors. These large tumours are being traumatically compressed by routine presurgical mammography, despite such investigation having no role in changing the therapeutic strategy. The commandments of meticulous oncological surgery are not being stressed[89]. Fisher's hypothesis of biological predeterminism has tended to minimize the importance of locoregional treatment. Furthermore, available intra-operative manoeuvres have not been sufficiently successful to prevent local recurrence. For example, the 'no-touch technique' long advocated in surgery for colonic cancer does not result in any significant improvement in local recurrence rates when compared with other surgical techniques[90]. Irrigation of the tumour bed with water decreases the number of cancer cells remaining in the wound; however, it does not appreciably change the rate of tumour colonization[57,73,91]. These examples suggest that intraoperative manoeuvres that decrease the number of free-floating tumour cells at the operative site still may not be sufficient to prevent local recurrence. Advantage must be taken of the knowledge that shed tumour cells are vulnerable before they acquire the ability to adhere to exposed connective tissue proteins in injured tissue and derive support from a wound's microenvironment of nurturing growth factors and other cytokines. Furthermore, residual microscopic foci of cancer distinct from the index tumour may be stimulated from a dormant state into active proliferation by these same growth factors. Research efforts must be devoted to neoadjuvant[92,93] and perioperative[85,94,95] measures that destroy free circulating tumour cells, that block cancer cell attachment to the extracellular matrix of the wound[96,97] or that modulate the growth factor environment without compromising the healing process itself.

In brief, a new paradigm is evolving based on the local production of tissue growth factors and cytokines in the operative wound to explain the previously unaccountable phenomenon of local recurrence. These factors are capable of attracting and stimulating free (unestablished), locally shed or systemically shed cancer cells at the wound site. Also they are capable of stimulating residual (established) cancer cells left in the breast adjacent to the operative wound. Oncological principles relating to cancer surgery are important and need to be re-emphasized. However, the best surgical results will not be achieved without simultaneous development of optimal neoadjuvant or perioperative treatment to nullify the effects of growth factors and cytokines on cancer cell survival and proliferation.

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Review

Molecular genetic basis of colorectal cancer susceptibility

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The past decade has seen considerable advances in understanding of the molecular processes involved in the development of colorectal cancer. With an increased awareness of genetic aspects of the disease there have already been significant changes in clinical management. This is exemplified by familial adenomatous polyposis, where identification of mutations in the adenomatous polyposis coli (*APC*) gene in affected individuals can be used directly to reduce the requirement for clinical screening in at-risk relatives. In other more common but less well defined heritable forms of colorectal cancer, testing to identify individuals for early diagnosis and treatment will soon become routine practice. This review does not set out to discuss all aspects of the molecular genetics of colorectal cancer but concentrates on the roles of the *APC* gene and the recently discovered DNA mismatch repair genes in colorectal cancer. The identification of these genes and their functional significance in the neoplastic process is discussed, and the relevance of such discoveries to future research and clinical management explored.

Colorectal cancer is the commonest cause of death due to malignancy in non-smokers in western countries and consumes considerable health care resources. There has been marginal improvement in survival from the disease in the past 50 years, mostly attributable to reduction in perioperative death resulting from advances in surgical technique and anaesthesia. This improvement has been offset by an increase in incidence of colorectal cancer and it is clear that prevailing clinical approaches often fail to influence the natural history of the disease. Presentation with late stage disease is common and the overall 5-year survival rate from population data is 37 per cent[1]; current treatment modalities of surgery, adjuvant chemotherapy and radiotherapy frequently offer no hope of cure. There is a need to improve understanding of the fundamental mechanisms of colorectal carcinogenesis to facilitate development of new approaches aimed at arresting and even preventing the malignant process. Identification of those individuals who are at high risk of developing the disease may allow the application of prophylactic measures such as chemoprevention, endoscopic polypectomy and even colectomy.

This review discusses two syndromes responsible for the majority of known genetic susceptibility to colorectal cancer, namely familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). Because of effective prophylaxis, patients with FAP should now account for fewer than 0·2 per cent of colorectal cancers. However, HNPCC constitutes a significant proportion of the disease with 2–5 per cent of patients with colorectal cancer fulfilling criteria for definition of the syndrome of HNPCC[2]. These stringent criteria were designed to select kindreds suitable for genetic research rather than provide diagnostic criteria relevant to clinical practice. As a consequence, the prevalence of HNPCC is likely to be underestimated when such empirical criteria are employed. Indeed, there is evidence to suggest that a substantial majority of large bowel tumours arise as a result of heritable susceptibility traits[3]. Complete characterization of susceptibility genes will allow the identification of individuals at high risk of developing colorectal cancer, such that genetic and clinical screening may be targeted. Understanding the function of such genes also offers hope for the rational development of therapeutic agents capable of interfering with the process of malignant transformation.

The *APC* gene and FAP

FAP results from germline mutations in the adenomatous polyposis coli (*APC*) gene. *APC* was localized to the long arm of chromosome 5 by genetic linkage analysis[4,5] following a clue from cytogenetic studies which noted a chromosomal deletion in a patient with FAP. A positional cloning strategy was then adopted by a number of groups and eventually the gene was cloned, sequenced and mutations identified in FAP kindreds[6–9]. Somatic mutations in the *APC* gene have been detected in early adenomas[10] and even in dysplastic aberrant crypt foci[11] which are believed to be precursors of adenomas[12]. This suggests that the initiation of adenoma formation in FAP requires inactivation of both copies of *APC*. This is supported by research in the multiple intestinal neoplasia (Min) mouse model of human FAP in which the remaining copy of the *APC* gene is also inactivated in adenomas which arise in the murine intestine[10,13]. In sporadic, non-polyposis neoplasms, inactivation of *APC* has also been demonstrated in the majority of carcinomas and the very smallest premalignant adenomas[14,15]. The combination of the causative role of *APC* gene mutations in the FAP syndrome and the detection of *APC* mutations at the very earliest stages of colorectal neoplasia indicates the pivotal role of *APC* mutations in the genesis of colorectal cancer.

APC *gene: structure and function*

APC is a large gene consisting of 15 exons encoding a protein containing 2843 amino acid residues Exons 1–14 are small, while exon 15 is large, accounting for 77 per

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cent of the coding region. Antibodies to the APC protein have identified a 300 kDa cytoplasmic protein expressed in epithelial cells[16]. This protein has been shown to associate with alpha- and beta-catenins which are known to bind to the cell surface molecule E-cadherin and are essential for its role in cellular adhesion. It is proposed that APC protein may affect the interaction between catenins and E-cadherin, thus influencing cellular adhesion and possibly intercellular communication[17,18]. Further subcellular localization has demonstrated that wild type APC binds to microtubules and may be important in their formation[19,20]. However, mutant APC product (missing the carboxyl terminal part of the molecule as a result of premature truncation) appears to lack this ability[19]. The organization and structure of microtubules are vital to cell division and there is speculation that the association of APC with the catenins, and hence cadherin, may afford a direct intracellular line of communication from cell surface to microtubule formation. In view of the central role in the development of colorectal cancer, further study to elucidate *APC* gene function holds great potential for understanding the fundamental basis of tumour formation. In the future, it may be possible to augment or replace the function of *APC* by pharmacological means in those with germline *APC* mutation or even prevent neoplastic change in the general population.

APC *mutational spectrum*

Inactivation of *APC* function is universal in both FAP and sporadic colorectal neoplasia. This occurs most frequently by mutations which create premature stop codons (i.e. the base triplet sequence TAG, TAA or TGA). This results in a premature signal for the endpoint of translation, resulting in the generation of a truncated protein product. The mutations are mainly deletions or insertions of short sequences, suggesting errors of replication rather than the action of mutagens[21]. Single nucleotide substitutions (most commonly C to T transitions) account for around 40 per cent of germline mutations already identified. In both FAP and sporadic colorectal neoplasms, 97 per cent of mutations occur in the 5' half of the gene and 60 per cent in a region of 600 codons within exon 15. Of the mutations responsible for FAP, 10–20 per cent[21] are short deletions at codons 1061 and 1309. Mutation analysis of over 800 FAP kindreds has been reported in the world literature and the overall frequency of identifying the causative mutation is only 30 per cent[21], ranging from 21 per cent[22] to 67 per cent[23]. This relatively poor rate of mutation detection reflects a number of factors including the selection criteria for the diagnosis of FAP, the sensitivity and robustness of the mutation detection technique employed and the assiduousness of the search for mutations. In dedicated laboratories, employing multiple methods of *APC* mutation analysis, detection rates of up to 90 per cent may be possible[24].

Identification of the *APC* gene mutation responsible for the FAP syndrome in any particular family is time-consuming and laborious. This has led to the development of functional assays for *APC* mutation detection which capitalize on the core defect of causative *APC* mutations, namely premature truncation of the protein product. One such technique involves *in vitro* synthesis of APC protein from patient DNA[24,25]. The presence of an *APC* gene mutation is indicated by the detection of truncated protein on electrophoresis. This protein truncation test is a rapid and efficient means of obtaining *de facto* evidence of the presence of a truncating and therefore causative mutation. The mutation can be fairly accurately localized using well characterized mutations as controls and then sequencing the relevant segment if so desired.

Genotype–phenotype correlations in FAP

It is becoming clear that the location of mutations within the *APC* gene has important clinical implications in terms of the colonic and extracolonic manifestations of FAP. Some appreciation of how mutation site could have an impact on clinical presentation can be gained from understanding the molecular biology of the APC protein interaction. Normal APC protein molecules are believed to function as dimers. However, mutant APC protein has been shown to interact with normal APC, blocking normal APC function[26]. The extent to which normal APC function is impaired may be related to the structure and residual ability of the mutant protein to form dimers. Severely truncated APC protein, due to mutations occurring in the most proximal part of the gene, may be incapable of binding with wild type APC. More distal 3' mutations allow translation of a larger protein structure containing the repeat sequences which permit heterodimer formation, resulting in impaired APC function. It may be predicted that a more aggressive phenotype will result from distal 3' mutations where overall APC function is impaired. Observational data bear this out, suggesting a functional boundary between codons 157 and 168 in exon 4 (*Fig. 1*). FAP families with an attenuated, usually late onset, disease have truncating mutations upstream of this boundary[27]. In contrast, mutations in the region between codons 1250 and 1464 (exon 15) result in an extreme phenotype with profuse early onset polyps in the colon and rectum[23,28]. These findings support the notion of a dominant-negative effect of truncating *APC* gene mutations, but other factors are certainly involved.

The phenotypic effects of mutations at different locations in *APC* are also demonstrated in the extent of extracolonic manifestations in FAP (*Fig. 1*). For some time, congenital hypertrophy of the retinal pigment epithelium (CHRPE) has been recognized as a common sign in FAP[29]. Olschwang *et al.*[30] defined a critical boundary in exon 9 with mutations 3' to this region associated with CHRPE lesions, whereas 5' mutations are associated with a normal retina. More recently, further data suggest that mutations occurring in the region between codons 1445 and 1578 in exon 15 do not induce the CHRPE phenotype[31] (*Fig. 1*). Although CHRPE lesions are themselves harmless, these findings are of considerable clinical relevance. Their association with a particular spectrum of mutation will permit the presence or absence of CHRPE lesions to guide the search for causative mutations in FAP families, thereby limiting the laborious and time-consuming analyses and providing more rapid results.

An inverse relationship between the presence of CHRPE lesions and desmoid tumours was suggested by Hodgson *et al.*[32], and recently Caspari *et al.*[31] provided mutation data supporting this relationship. The majority of individuals with mutations between codons 1445 and 1578 showing no CHRPE lesions had desmoid tumours. Furthermore, these desmoids tended to be aggressive, often predated symptomatic colorectal disease and, in some cases, resulted directly in death. Clearly, the ability

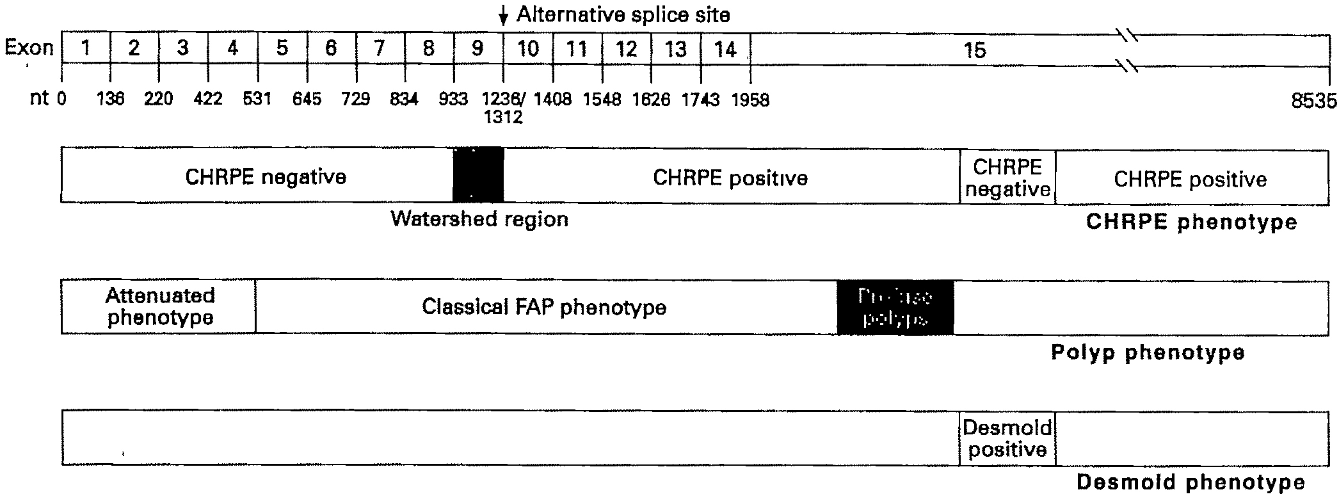

Fig. 1 Schematic diagram of the *APC* gene, with labelling of 15 exons and 8535 nucleotides Congenital hypertrophy of the retinal pigment epithelium (CHRPE), colorectal polyp and desmoid phenotypes are described in horizontal bars corresponding to regions of the *APC* gene in which causative mutations have been described. FAP, familial adenomatous polyposis

to predict the clinical course in FAP on the basis of causative mutations will have significant effects on clinical management and patient counselling. Those with mutations predicted to result in uncontrollable rectal polyps (e.g. deletion at codon 1309) may be better served by restorative proctocolectomy with ileoanal pouch rather than by colectomy and ileorectal anastomosis. Antenatal diagnosis in FAP is a highly contentious area, but those individuals whose mutations are associated with severe, debilitating disease may wish to ensure that offspring are not affected. In the longer term, as the number of reported mutations increases and the quality of clinical data improves, complete elucidation of the clinical effects of different *APC* gene mutations will be of great value, yielding clues to the functional significance of various domains of the APC protein and ultimately means by which therapeutic intervention may succeed.

Other genetic and environmental phenotypic modifiers are suggested by the fact that identical *APC* gene mutations have been associated with diverse FAP phenotypes[33,34]. It is clear that environmental modulation does occur since a reduction in number and size of colorectal polyps can be achieved following treatment with the non-steroidal anti-inflammatory agent sulindac[35]. In addition, alteration of the rectal milieu after colectomy and ileorectal anastomosis is associated with regression of rectal polyps[36]. There is evidence from the Min mouse[37] model of FAP that phenotypic expression is modified by a locus[38] on mouse chromosome 4 corresponding to human chromosome region 1p35–36. Interestingly, this chromosomal region has been noted to exhibit deletion or rearrangement in sporadic colorectal tumour tissue. Characterization of such a modifier gene may allow pharmacological modulation of the FAP phenotype.

Predictive genetic testing for FAP

As a direct consequence of identification of *APC*, it became possible to perform accurate predictive testing for FAP. This can employ either genetic linkage analysis or mutation analysis. In linkage analysis, markers near the *APC* gene are traced through a family to give an assessment of the risk of gene inheritance. Mutation analysis involves identification of the causative mutation within the *APC* gene sequence of the affected individual. Linkage analysis has been shown to be of considerable practical value in FAP predictive testing[39] and the recent availability of highly polymorphic microsatellite markers has increased its predictive power. However, it suffers from several handicaps. The analysis requires DNA from two affected individuals in the family, which restricts its application. Early death of gene carriers, uncertain paternity within families and the fact that around 25 per cent of FAP patients carry a new mutation with no family history, reduces the value of linkage studies in many clinical situations. Furthermore, by its nature, linkage analysis provides only an estimation of risk of being a gene carrier rather than a definitive diagnosis. Consequently, linkage analysis is reserved for those families in which the causative *APC* mutation eludes detection.

Mutation analysis does not suffer the restrictions of linkage analysis and is undoubtedly the optimal means of predictive testing in FAP. It offers a firm diagnosis in members of a FAP family in whom the *APC* mutation has been characterized. Those individuals proven to be non-gene carriers need never be enrolled in clinical screening programmes, resulting in reduction in patient distress and health care expenditure. Individuals found to carry an *APC* mutation are provided with appropriate counselling. Prophylactic surgery can then be planned, taking account of the predicted phenotype of the mutation along with the patient's aspirations in education, partnerships and reproduction.

In the longer term, understanding the molecular mechanisms involved in FAP will lead to novel therapeutic approaches manipulating the disease process. While the benefits of prophylactic colectomy are unlikely to be supplanted, we may hope that the devastating effects of extracolonic disease such as desmoid tumours and upper gastrointestinal malignancy will be controlled. It is also reasonable to speculate that treatment of sporadic, non-FAP colorectal cancer will also be enhanced by such developments.

DNA mismatch repair genes in hereditary non-polyposis colorectal cancer

Phenotype and penetrance of HNPCC

Elucidation of the genetic basis of FAP was aided by the clear association of myriads of adenomas, subsequent cancer risk and the presence of a highly penetrant single gene disorder. In contrast, there are no clinical features which are pathognomonic of HNPCC other than early onset cancer with a familial aggregation. Four different genes have been implicated in the aetiology of HNPCC and penetrance is likely to be only 70–80 per cent (i.e. 20–30 per cent of individuals with a predisposing mutation may never develop cancer). Therefore, HNPCC presents a more elusive problem for the researcher and clinician. Cancers occurring as part of the HNPCC syndrome tend to arise in the proximal colon. In some families, colorectal cancer may be the only malignancy, while in others there is also segregation of uterine, ovarian, gastric, upper urinary tract, pancreatic, small bowel and skin cancers.

Fig. 2 shows an HNPCC kindred in which all six cases of colorectal cancer were of early onset, before 55 years of age. There are at least two unaffected presumptive obligate gene carriers in the second and third generations (II:4 and III:5), one of whom was elderly when she died from an unrelated condition and another who is as yet unaffected. This pedigree provides strong evidence that the penetrance of HNPCC gene mutations is lower than was widely believed. In addition, female gene carriers seem more protected from colorectal cancer than male gene carriers, suggesting the intriguing possibility of a sex-linked modifier gene. There is also evidence of co-segregation of early onset colorectal polyps and cases of colorectal, uterine and pancreatic cancers.

The prevalence of HNPCC is around 5 per cent; however, this is likely to be an underestimate since it is derived from the application of stringent criteria proposed by the International Collaborative Group on HNPCC[2]. These require: three or more relatives with histologically proven colorectal cancer, one being a first degree relative of the other two; two or more generations affected; and at least one family member affected before age 50 years. These criteria will identify only large families where the gene defect is highly penetrant; therefore many small families will be excluded inappropriately. When these criteria are loosened, the prevalence of HNPCC will increase with a corresponding decrease in the apparent penetrance of the gene defect(s). The true penetrance of HNPCC genes can be determined only through an extensive search for mutations in colorectal cancer families ascertained on a population basis.

HNPCC results from mutations in mismatch repair genes

Four human genes have recently been identified which, when mutated, result in predisposition to colorectal cancer which is hereditary. These genes are human homologues of yeast and bacterial DNA repair genes and are known as *h*MSH2 on chromosome 2p[40,41], *h*MLH1 on chromosome 3p[42–43], *h*PMS1 on chromosome 2q[44] and *h*PMS2 on chromosome 7q[44]. *h*MSH2 was originally localized to chromosome 2p by genetic linkage studies in two large unrelated HNPCC pedigrees[45]. A subsequent study reported linkage to a marker on chromosome 3p in another family[46], providing evidence for genetic heterogeneity in HNPCC. Several apparently diverse areas of research subsequently converged to elucidate the underlying functional defect in HNPCC and provide clues to the genes responsible.

Studies on repeat sequences in genomic DNA from cancers in HNPCC identified widespread instability in short repetitive tracts, suggestive of defective DNA mismatch repair[47–49]. A similar pattern of DNA instability was described in *Escherichia coli*[50] and yeast[51–53] when mutations were induced experimentally in mismatch repair genes. This group of genes became a strong candidate for the human condition of HNPCC with the characteristic change in repeat DNA. Efforts to isolate the genes responsible for HNPCC focused on identifying human homologues of the yeast and bacterial DNA mismatch repair genes.

The first to be isolated was *h*MSH2 on chromosome

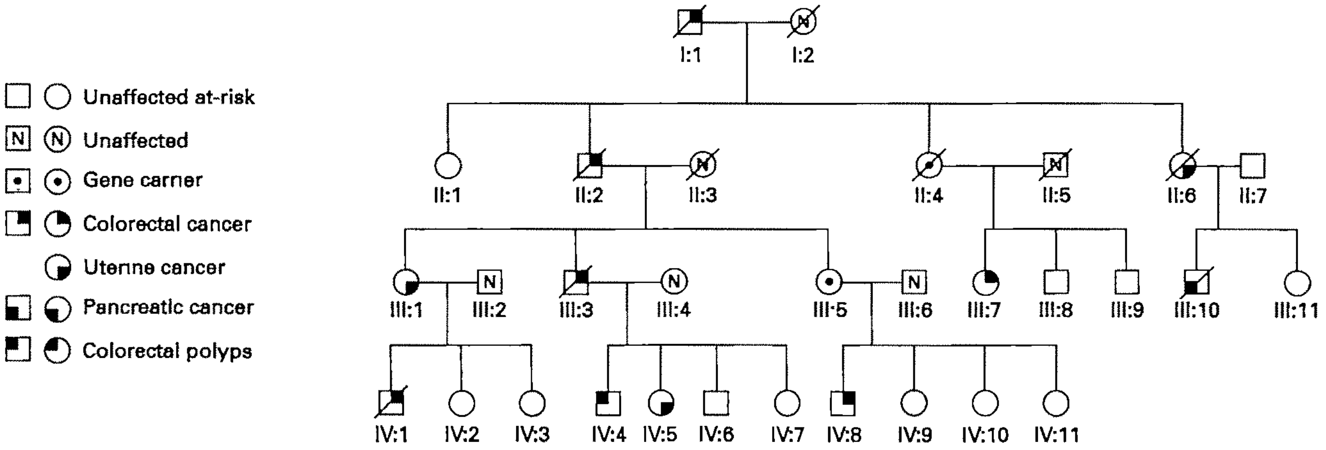

Fig. 2 A four generation family with hereditary non-polyposis colorectal cancer Women are represented by circles and men by squares. Diagonal line denotes dead. Further definitions are given in the key. All six cases of colorectal cancer were early onset and four arose proximal to the splenic flexure. In this family, colorectal cancer segregates with colorectal polyps and malignant disease of the uterus and pancreas. This pedigree displays incomplete penetrance, where females II.4 and III 5 were asymptomatic gene carriers, passing the causative mutation to their children

2p[40,41]. Fishel *et al.*[40] exploited the fact that genes with such fundamental function frequently display homology between species. Using DNA sequence from yeast, the human homologue *h*MSH2 was localized to chromosome 2p. Vogelstein's group (Leach *et al.*[41]) used detailed linkage studies to localize the gene, then screened candidate genes in that region for the presence of germline mutations in HNPCC kindreds. A 2802 nucleotide complementary DNA from *h*MSH2 was identified and mutations were shown to co-segregate with HNPCC in families linked to chromosome 2p.

Once it became clear that defects in mismatch repair were responsible for HNPCC, other genes with similar sequence and known to be involved in mismatch repair were identified and mutations demonstrated to be responsible for the HNPCC in other families. *h*MLH1 mutations were shown to be responsible for disease segregating with chromosome 3p markers[42,43], whereas, *h*PMS1 and *h*PMS2, on chromosomes 2q and 7q respectively, account for a proportion of remaining HNPCC families[44]. At this early stage there are only limited mutation data on *h*MLH1, *h*MSH2 and *h*PMS genes. These include nucleotide substitutions, short deletions and deletions of several hundred base pairs often with the creation of premature stop codons and generation of truncated protein.

More recently a further gene, *GTBP*, has been identified which is a member of the same family of genes as *h*MSH2. GTBP protein forms a complex with *h*MSH2 and this heterodimer, known as *h*MutSα, is essential for correcting subtle mismatch errors[54–56]. Mutations in *GTBP* are associated with defective mismatch repair in colorectal cancer cell lines; however, as yet, no germline mutations have been demonstrated in HNPCC[56]. At present, the *GTBP* gene is the focus of considerable research and its contribution to colorectal carcinogenesis is likely to be elucidated in the near future.

There are at least four genes responsible for HNPCC and this has important implications for HNPCC population genetics and screening. The true penetrance of HNPCC gene mutations is unknown and HNPCC gene frequency may well be substantially higher than the prevalence suggested by families selected through the International Collaborative Group criteria. Lynch *et al.*[57] have calculated that the population gene frequency may be around 1 in 200. It is possible that some individuals may carry mutations in two or more predisposition genes. Thus, in a family with a characterized mutation in *h*MSH2, some individuals may be reassured as being non-carriers and discharged from follow-up when, in fact, they have a coincidental mutation in *h*MLH1. Such a possibility demands extreme caution before widespread introduction of genetic screening for HNPCC. At present, it seems wise to recommend continued colonoscopic screening, even in those at-risk individuals who are shown to be non-gene carriers, until further information is produced regarding penetrance and potential effects of abnormalities in more than one mismatch repair gene.

DNA instability in HNPCC and 'sporadic' colorectal cancers

DNA from cancers associated with HNPCC displays a characteristic instability in repetitive DNA sequence as a result of replication errors[45,58,59]. *Fig. 3* compares three cancers, one of which displays instability at a microsatellite repeat locus. Each allelic band in normal DNA contains the repeat sequence, and in patients B and C these are identical in both normal and tumour DNA. However, in patient A there is a shift in the allele pattern in tumour DNA, consistent with microsatellite instability and indicating a replication error in this tumour. Such changes are also detectable in around 1 in 6 apparently sporadic colorectal cancers[47–49,60]. Such 'sporadic' tumours with DNA microsatellite instability tend to be right-sided, diploid, and have an inverse relationship with p53 mutation[58] – features which are shared with cancers arising in HNPCC. Surprisingly, there is no significant age difference between patients with tumours exhibiting microsatellite instability and those whose tumours do not[48,60]. However, 60 per cent of very young patients have been shown to have tumour DNA instability[61]. The inverse relationship between microsatellite instability and aneuploidy/p53 mutation suggests that one of two mechanisms is required in colorectal cancer development. One involves defects in mismatch repair in diploid cells, while the other involves p53 mutation and the development of aneuploidy[62].

Tumours with DNA instability may represent a useful marker of a subset of patients more likely to carry germline mismatch repair gene mutations. Liu *et al.*[63] found that 15 per cent of cancers displayed DNA instability but detected germline mutations in *h*MSH2 and *h*MLH1 in only 10 per cent of these. This low frequency suggests that defects in other mismatch repair systems may be involved. At present, it is appropriate to concentrate efforts on large cancer families and individuals with early onset

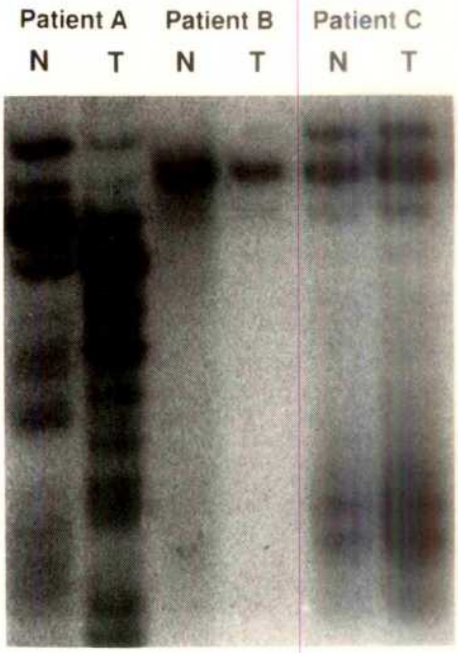

Fig. 3 Microsatellite instability in colorectal cancer DNA. Autoradiograph demonstrating microsatellite locus on chromosome 8 which is amplified by polymerase chain reaction and separated by polyacrylamide gel electrophoresis. Each allelic band in normal (N) DNA contains the repeat sequence (patients A and C are heterozygous, and B homozygous). In patients B and C, identical alleles are present in both normal and tumour (T) DNA. However, in patient A there is a shift in the allele pattern in tumour DNA, consistent with microsatellite instability at one allele and indicating a mismatch repair error in this tumour

disease where mutations in *h*MSH2 and *h*MLH1 are identified at higher frequency.

The detection of microsatellite instability in endometrial cancer[64] and in a number of cancers of different tissue origin in HNPCC gene carriers[59] is of great interest, as it demonstrates that the underlying HNPCC gene mutation is, indeed, responsible for the mutator phenotype. In addition, it has been shown that microsatellite instability occurs in tumours from patients with multiple different primary cancers[65], suggesting that such individuals may well carry DNA repair gene mutations even without a family history of cancer.

Mismatch repair defects in man and the adenoma–carcinoma sequence

*h*MSH2, *h*MLH1, *h*PMS1/2 and the newly discovered *GTBP* function in a coordinated fashion to recognize, excise and repair the mismatched sequence on newly formed strands of DNA. There may well be further mismatch repair systems involved in colorectal and other cancers. One such candidate is a nucleotide-specific mismatch repair system which recognizes G–T mismatches[66]. If uncorrected, these mismatches lead to a C to T transition. As previously discussed, such transitions are frequently seen in the *APC* gene in both FAP and sporadic colorectal tumours. This raises the intriguing possibility that many of the somatic changes that are involved in the very genesis of colorectal cancer and indeed of FAP are caused by defects in DNA repair systems.

Adenomas in patients carrying HNPCC gene mutations display microsatellite instability, suggesting that mismatch repair defects are important early events in colorectal carcinogenesis[59]. Tumour formation requires inactivation of both copies of a given mismatch repair gene, one copy by germline mutation and the other by somatic (acquired) mutation[41,43]. Colorectal cancer cell lines exhibiting microsatellite instability have a continuing defect in mismatch repair, which persists through transformation, leading to progressive alterations in repetitive DNA sequences[67–69]. It seems reasonable to speculate that in human cancers the functional defect in mismatch repair will also persist, leading to further mutations and genetic derangement.

There is substantial evidence to suggest that inactivation of both copies of a DNA repair gene by mutation, or loss of one gene copy, is required for tumour formation. However, it is also clear that a subtle phenotype is associated with heterozygous germline mutations, since abnormal colonic crypt cell production rate and DNA repair have been reported in the apparently normal colorectal mucosa of affected and at-risk HNPCC family members[70,71]. In addition, it has been shown that a subset of patients with germline mismatch repair gene mutations do, in fact, have an increased mutation rate in their normal tissues[67–72]. This is of considerable importance because such individuals have mutations developing in many tissues, but develop relatively few tumours. It may be that mutations must occur in important genes, such as *APC*, before a cancer can develop and it seems likely that environmental influences must have a major involvement in this process.

Research into the molecular basis of HNPCC has proceeded at a staggering pace and it will take some time for these developments to be appreciated and incorporated into routine clinical practice. However, HNPCC accounts for a significant proportion of colorectal cancer and there is every reason to hope that new approaches in management will lead to a reduction in cancer incidence in at-risk populations.

Other loci involved in genetic predisposition to colorectal cancer

Infidelity in other systems of DNA replication

Evidence of microsatellite instability has been demonstrated in over 60 per cent of patients presenting with colorectal cancer before the age of 35 years. This group would be expected to have constitutional predisposition to their disease and, indeed, extensive mutation analysis has revealed mismatch repair mutations in 60 per cent[61]. However, this presents the problem that the other 40 per cent are caused by as yet undetermined factors. It seems likely that a substantial proportion of such early onset cases are indeed due to genetic predisposition, but the genes involved remain to be identified. One candidate group involves the nucleotide-specific mismatch repair system which recognizes G–T mismatches[66]. Others may result from inherited defects in DNA polymerases, such as polymerase δ. Recent reports of colorectal cancer cell lines have identified microsatellite instability associated with polymerase δ in the absence of mismatch repair gene mutations[73]. These findings support the existence of considerable genetic heterogeneity in colorectal cancer predisposition and, particularly, infidelity in DNA replication.

The ras *genes*

Activated proto-oncogenes have been shown to play a major role in many human cancers[74]. The *ras* gene family are cytoplasmic proto-oncogenes with signal transduction functions. Activating mutations in codons 12 and 13 of Kirsten *ras* occur in 50 per cent of colorectal cancers and adenomas greater than 1 cm in diameter[74]. The frequency of K-*ras* mutations is much lower in adenomas less than 1 cm, which suggests that this oncogene is involved in the progression of adenoma to carcinoma[75]. K-*ras* expression, although high in primary carcinomas, tends to be lower in clinically advanced cases, indicating that when the tumour progresses to a certain stage *ras* activation is no longer required.

There is some evidence to suggest that *ras* genes may be involved in colorectal cancer susceptibility. A meta-analysis of all published studies identified rare Harvey *ras* alleles as likely predisposition factors in cancer and from their findings the authors propose that 1 in 11 colorectal cancers occurs as a result of inheritance of a predisposing H-*ras* allele[76]. It is possible that inheritance of a rare H-*ras* allele may indicate an increased risk of colorectal cancer which may even interact with predisposition due to inheritance of a *h*MSH2 or other DNA repair gene mutation.

Perspective

This review has summarized the more clinically relevant aspects of current research in molecular genetics of colorectal cancer, with particular regard to HNPCC and FAP. The contributions of other important genes involved in colorectal cancer, including p53 and *DCC*, have not been considered but the events described above must be taken in the context of alterations in these genes[74]. The central roles of *APC* and the mutator genes in colorectal cancer are clear. It is even possible that changes in other cancer genes may be induced by defects in mismatch repair.

The clinical relevance of genetic studies of the *APC* gene in FAP is now beyond doubt. However, in numerical terms, HNPCC is of far greater importance than FAP. As the molecular basis of HNPCC is unravelled, it will have considerable influence on colorectal cancer screening; this may lead to a rational approach to population screening for predisposition genes.

Screening for gene carriers in HNPCC

There is widespread interest among clinicians and the public over genetic susceptibility to colorectal cancer. This has forced a substantial increase in colonoscopic screening solely on the basis of a family history of the disease. The reality is that the majority of individuals with a family history of large bowel cancer are not at substantial risk of the disease. Thus, there is a clear need to identify HNPCC gene carriers systematically, focusing clinical screening on these individuals who have greater than 70 per cent chance of developing the disease.

The possibility of population screening for HNPCC has been alluded to above. However, the number of genes involved and the variety of mutations responsible militate against non-selective screening of the general population. A practical approach to genetic screening may exploit the fact that all tumours from patients with proven germline mismatch repair gene defects have microsatellite instability[48]. All colorectal cancer patients coming into pathology departments could undergo routine assessment for microsatellite instability. Individuals with tumours showing evidence of mismatch repair could be targeted for mutation screening of *h*MSH2, *h*MLH1, *h*PMS1/2, *GTBP* and other candidate genes as they are identified. Thus, microsatellite instability could be used as a biomarker indicating an increased likelihood that the cancer host carries an inherited HNPCC gene mutation. Those shown to have germline mutations could be counselled with a view to offering clinical and genetic screening to their relatives. This would allow efficient targeting of long-term colonoscopic screening to those who most need it. At present, this screening is recommended every 3 years, but recent investigations in high-risk individuals support a more intensive approach with colonoscopy every 1–2 years[77,78]. As such screening may last up to 50 years, the burden in terms of cost and patient morbidity could be considerable and these difficulties may be addressed only by prophylactic measures. However, unlike FAP, the absence of a definite premalignant phenotype in HNPCC and the present uncertainty over gene penetrance make prophylactic colectomy unappealing. Fortunately, it is likely that these problems will be resolved in the near future, leading to novel approaches in the management of HNPCC and indeed other cancers.

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Long-term outcome after surgery for asymptomatic small hepatocellular carcinoma

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The subjects of this study were 48 asymptomatic patients who had surgery for small hepatocellar carcinoma (HCC). There were 42 men and six women with mean(s.d.) tumour size of 3·31(1·46) cm and age 55·0(7·4) years. Follow-up was for a minimum of 10 years. The main concern of this study was a univariate analysis of factors that might affect long-term survival after surgery, which was 50 per cent at 5 years and 31 per cent at 10 years. A high incidence of recurrent HCC (37 of 48 patients) was observed but reoperation further prolonged life in some cases. The significant prognostic factors detected by multivariate analysis were: histological classification, functional liver reserve and histology of the resection margin. Tumour size, gross appearance of tumour, presence of liver cirrhosis, serum α-fetoprotein level, age or sex did not affect the prognosis.

The close relationship between hepatocellular carcinoma (HCC) and hepatitis B virus has been confirmed by geographical survey[1], histological examination of HCC specimens[2], serological study of patients with HCC[3,4] and epidemiological data[5]. Hepatitis B surface antigen carriers and patients with either liver cirrhosis or a family history of HCC[6] are at high risk of developing this lesion. The screening procedure among high-risk individuals is liver ultrasonographic examination and/or measurement of serum α-fetoprotein (AFP) level. Once a liver tumour is detected the nature of the lesion is confirmed by a computed tomography and hepatic angiography.

Recent advances in resection techniques on cirrhotic liver[7] have resulted in a number of patients with small HCC receiving surgery. Some 15 years have passed since the first operation for asymptomatic small HCC was performed at this centre. The present study was designed to determine late outcome and to evaluate prognostic factors associated with long survival.

Patients and methods

Forty-eight patients with histologically proven HCC who had a surgical resection in the Department of Surgery, National Taiwan University Hospital between April 1979 and April 1984 were included in the study There were 42 men and six women of mean(s.d.) age 55·0(7·4) years with a mean(s.d.) tumour size of 3·31(1·46) cm. Patients who had inadequate histological classification, and those who died from causes unrelated to HCC or from HCC due to tumour implantation into the biopsy tract, were excluded. Surgical resection was not considered for patients with more than two tumours in the liver or evidence of hepatic decompensation. Cirrhosis of the liver was confirmed by liver biopsy taken adjacent to the tumour.

The surgical technique used was non-anatomical, using Lin's hepatic clamp plus finger dissection for lesions distant from the hilar area[7]. Temporary clamping of the hepatic artery, or Pringle's manoeuvre, was used before applying finger dissection for lesions either close to the hilar area or those to which a hepatic clamp could not be applied.

All patients were followed until death or to the end of April 1994, 120 months after the last patient was included in the series. Maximum follow-up was 180 months. No patient was lost to follow-up.

Survival analysis

The following factors that might have influenced long-term survival were assessed: age, sex, tumour appearance, resection margin, histological classification, tumour size, 45-min bromsulphaphthalein (BSP) retention rate, presence of liver cirrhosis and serum AFP level. In evaluating tumour appearance, a round shape with capsule formation and a homogeneous cut surface was considered typical. An irregular tumour appearance either with or without a capsule and a heterogeneous cut surface, or satellite nodule formation, or tumour invasion of a branch of the portal vein was classified as atypical[6]. The resection margin was defined as the shortest distance between the resected liver margin and tumour margin and was classified into two groups: less than or equal to 1 cm, and greater than 1 cm. Histological findings were classified into three groups: (a) encapsulated tumour without extracapsular tumour invasion; (b) encapsulated tumour with extracapsular invasion; and (c) tumour without a capsule. The largest diameter of the tumour was divided into two subgroups: greater than 3 cm, and less than or equal to 3 cm. The liver reserve was expressed as the 45-min serum BSP retention rate and was similarly divided into two subgroups: over 11 per cent, and less than or equal to 11 per cent. Liver biopsy established that 40 patients had liver cirrhosis, three portal fibrosis and the remainder were normal. Serum AFP was classified into three subgroups: less than 20 ng/ml (normal range), between 20 and 1000 ng/ml, and over 1000 ng/ml.

Survival analysis was used to determine statistical differences between prognostic variables, using the Biomedical program 2L Statistical Software (University of California, Los Angeles, California, USA). The nine factors assessed were analysed using the univariate log rank test. Significant prognostic factors identified through stepwise selection were entered into the final Cox proportional hazards model for multivariate analysis.

Results

The survival rate of 48 patients with asymptomatic small HCC was 50 per cent (24 patients) after 5 years and 31 per cent (15 patients) after 10 years (*Fig. 1*). Fifteen patients were alive at the end of this study. All patients who died had recurrent HCC. Recurrent HCC was noted in 37 of 48 patients. The site of recurrence was the liver remnant in all 37 patients, but two had lung or skull bone metastases in addition. Reoperation was performed on ten patients. Among the surviving patients, three had received a second operation and one a third procedure for recurrent HCC. Among those who died, six received a second operation for recurrent HCC (*Table 1*). A

Professor C.-S. Lee died suddenly on 13 February 1995.

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significantly longer survival was observed in patients who had had more than one hepatic resection, both in survivors (range 24–129 months) and non-survivors (range 16–44 months). Three factors (histological classification, BSP retention rate and resection margin) were significantly related to survival when evaluated by univariate analysis (*Table 2*). All three factors were selected to enter the final Cox proportional hazards model for multivariate analysis (*Table 3*). Eight patients with encapsulated tumour and no extracapsular tumour invasion had the best outcome with a mean survival time of 145 months (*Fig. 2*). The hazard ratio of patients with encapsulated tumours *versus* those with capsular invasion was 4·34 ($P = 0{\cdot}026$), and that between patients with tumours without a capsule *versus* those with encapsulated tumours was 11·18 ($P = 0{\cdot}002$). Patients with improved liver reserve (BSP retention rate less than or equal to 11 per cent; $n = 18$) had a better long-term survival (mean(s.e.m.) 113(17) months) than those with poor liver reserve (BSP retention rate over 11 per cent; $n = 30$) who had a mean(s.e.m.) survival of 70(10) months ($P = 0{\cdot}02$) (*Table 2*). The hazard ratio was 1·06 for poor compared with improved liver reserve (*Table 3*). Patients ($n = 10$) with a tumour resection margin less than or equal to 1 cm had a poorer prognosis (mean(s.e.m.) survival 52(14) months) than those with a resection margin greater than 1 cm ($n = 38$; mean(s.e.m.) survival 98(12) months) ($P = 0{\cdot}04$).

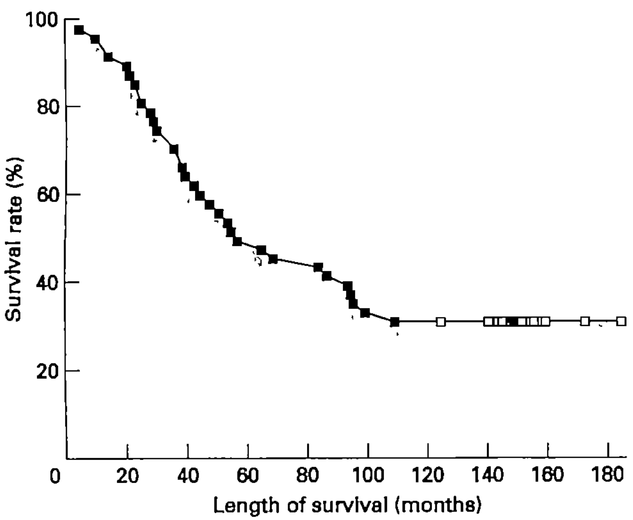

Fig. 1 Survival curve of 48 patients with asymptomatic small hepatocellular carcinoma (HCC) after surgical resection. Thirty-three patients died from recurrent HCC (■)and 15 are still alive and well (□). The 5- and 10-year survival rates were 50 and 31 per cent respectively

Table 2 Univariate analysis of prognostic factors for long-term survival

	No of patients	Survival time (months)*	*P*†
Histological classification			
Tumour without extracapsular invasion	8	145(22)	
Tumour with extracapsular invasion	32	82(11)	0·02
Tumour without capsule	8	47(12)	
BSP retention rate (%)			
≤11	18	113(17)	0·02
>11	30	70(10)	
Gross appearance of tumour			
Typical	25	104(14)	0·12
Atypical	23	70(12)	
Liver cirrhosis			
Cirrhosis	40	84(10)	0·35
No cirrhosis	8	105(28)	
Tumour size (cm)			
>3	26	92(14)	0·35
≤3	22	78(12)	
Resection margin (cm)			
>1	38	98(12)	0·04
≤1	10	52(14)	
Serum AFP (ng/ml)			
<20	9	59(19)	
20–1000	24	101(14)	0·35
>1000	15	75(15)	
Age (years)			
>51	37	96(11)	0·15
≤51	11	58(16)	
Sex			
Male	42	89(11)	0·98
Female	6	82(27)	

*Values are mean(s.e.m.). AFP, α-fetoprotein; BSP, bromsulphaphthalein. †Mantel Cox statistic

Table 1 Outcome of patients who had more than one hepatic resection for hepatocellular carcinoma

Patient no.	Interval between first and second operations (months)	Interval between second and third operations (months)	Survival after the second operation (months)	Present status
1	15	—	129	Alive and well after 144 months
2	36	—	120	Alive and well after 156 months
3	156	—	24	Alive and well after 180 months
4	122	18	27	Alive and well after 149 months
5	6	—	17	Died
6	9	—	34	Died
7	24	—	18	Died
8	35	—	16	Died
9	48	—	44	Died
10	69	—	36	Died

Table 3 Multivariate analysis of three significant prognostic factors identified by univariate analysis

	Regression coefficient (β)	Standard error	P*	Hazard ratio
Histological classification				
Tumour without extracapsular invasion (a)	1·468 (a *versus* b)	0·661	0·026	4·34 (1·19–15·84)
Tumour with extracapsular invasion (b)	2·414 (a *versus* c)	0·769	0·002	11·18 (2·47–50·50)
Tumour without capsule (c)				
BSP retention rate (each subgroup with 1 per cent difference)	0·057	0·029	0·048	1·06 (1·00–1·12)
Resection margin (cm)				
>1				
≤1	0·910	0·433	0·036	2·48 (1·06–5·80)

Values in parentheses are 95 per cent confidence intervals. BSP, bromsulphaphthalein. *Cox proportional hazards survival analysis

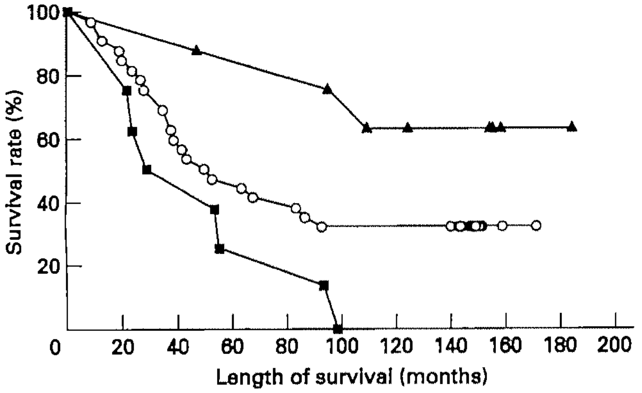

Fig. 2 The outcome of patients with hepatocellular carcinoma classified by histology. ▲, Tumours without extracapsular invasion; ○, tumours with extracapsular invasion; ■, tumours without a capsule

None of the other factors evaluated significantly affected survival.

Discussion

The survival rate from small HCC of 50 per cent at 5 years and 31 per cent at 10 years in this study corresponded to the 68 per cent reported from China[8] but was different from the values of 19 and 38 per cent (after 4 years) reported from Japan[9,10]. This might be explained by the higher incidence of hepatitis B virus (80–90 per cent) in Taiwanese and Chinese patients and by the higher association of hepatitis C virus (70–76 per cent) in Japanese patients.

All deaths in this series were from recurrent HCC and reoperation was needed to achieve a survival rate of 30 per cent at 10 years. Others[11] have reported a cumulative recurrence rate of 72 per cent, 3 years after resection of HCC in the size range 1–16 cm. The timing of recurrence has been reported to relate to the size of the primary tumour[12]. A high recurrence rate was observed in this study despite the small tumour size, because of the prolonged follow-up. The aggressive nature of HCC might be explained if small lesions were not detected by preoperative hepatic angiography which then resulted in early recurrent HCC, within as little as 3 months of initial surgery in some patients. Local tumour invasion was probably the cause of recurrence in tumours without a capsule or with extracapsular invasion. Another possibility, suggested by recurrence of HCC as late as 13 years after initial surgery, is that there was a second primary tumour owing to multifocal disease[13]. Reoperation for recurrent HCC prolonged the patient's life irrespective of the interval between first and second operations (*Table 1*).

Gross tumour appearance (typical or atypical) was a significant prognostic factor in symptomatic large HCC[6], but not for small HCC in this study. Non-capsulated tumours had a 100 per cent recurrence rate, whereas tumours with a capsule and no extracapsular invasion fared best, in agreement with previous reports[14–17]. Long-term survivors from large HCC reported in the 1970s[18] probably belonged to the latter group. The different biological behaviour of small HCC should be considered in the assessment of any therapeutic trial involving procedures such as transarterial embolization, chemoimmunotherapy and orthotopic liver transplantation. Liver transplantation in patients with cirrhosis and HCC yielded similar results to those of hepatic resection (47 *versus* 50 per cent respectively at 3 years)[19]. Persistence of hepatis B virus after liver transplantation and the increased incidence of HCC after long-term immunosuppression[20] mean that hepatic resection is the treatment of choice for patients with operable tumours. Liver transplantation may be reserved for patients with recurrent HCC.

The presence of liver cirrhosis was not a significant prognostic factor[8,21], but more precise evaluation of liver function indicated a close relationship between outcome and liver reserve, as reported previously[10,16]. The screening of patients with cirrhosis revealed a large proportion with HCC and poor liver reserve, which significantly affected the surgical outcome.

There is controversy about the relationship between tumour size and prognosis. Although some reports indicate that size is a significant factor[8,22], most authors[6,23,24] do not agree. The main reason for the discrepancy might be the method of evaluation (univariate *versus* multivariate analysis) or the way in which tumours are grouped by size. Tumour diameter above 1 cm was not a significant prognostic factor[6], which implies that size should not be used in the staging of small HCC.

It has been reported that a clear resection margin of more than 1 cm is a significant prognostic factor[6,24]. This was confirmed by multivariate analysis in the present study. However, different resection margins might be necessary depending on the presence of extracapsular tumour invasion. A wide resection margin is probably not necessary for patients without extracapsular tumour invasion[25]. Therefore, the size of resection margin should be decided on an individual basis.

Extensive resources are required to screen individuals at high risk of HCC. These include patients with cirrhosis, hepatitis B surface antigen carriers, and those with a family history of HCC[6]. Half of the patients diagnosed with asymptomatic small HCC will not be considered for surgery because they have poor liver reserve, multiple lesions or an infiltrative type of HCC. The long-term outcome of resected patients offered hope, but the high recurrence rate (37 of 48 patients over 10 years) frustrated the screening programme. The two extreme outcomes of HCC, depending on the histological classification, illustrate the variable biological behaviour of small HCC. The best hope of improving outcome from HCC is to identify the carcinogen that appears to escape detoxification in cirrhotic liver (in addition to hepatitis B) and to investigate further the biological behaviour of the tumour. The formidable programme of vaccination of babies from mothers infected with hepatitis B virus, which is already under way in this country, may reduce the incidence of HCC in the next generation.

Acknowledgements

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Short note

Laparoscopic resection of solid liver tumours

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Laparoscopic surgical treatment of abdominal disorders such as cholelithiasis is now accepted[1]. For technical reasons laparoscopic liver surgery has been slow to develop. Early reports involved surgery for biliary and hydatid cyst[2,3]. Increasing sophistication in laparoscopic instrumentation and surgical skills has now made videolaparoscopic resection of liver tumours feasible. In this report one patient with a liver metastasis and two with focal nodular hyperplasia underwent resection under videolaparoscopy.

Patients and methods

The three patients studied were women aged 47, 44 and 33 years. Abdominal ultrasonography and computed tomography in patient 1 showed a 4-cm superficial metastasis of liver segment IV, 4 years after mastectomy for a $pT_2N_0M_0$ ductal carcinoma. Patient 2 presented with symptomatic cholelithiasis and an 8-cm liver mass involving segments II and III. After ultrasonography, computed tomography and percutaneous biopsy, hepatocellular carcinoma could not be excluded. In patient 3, ultrasonography, computed tomography and arteriography showed a 4-cm hepatic mass involving liver segment III. Liver function tests and tumour markers (carcinoembryonic antigen and CA 15-3) were normal in all three patients. Patients 2 and 3 had been taking oral contraceptives for 15 and 16 years respectively.

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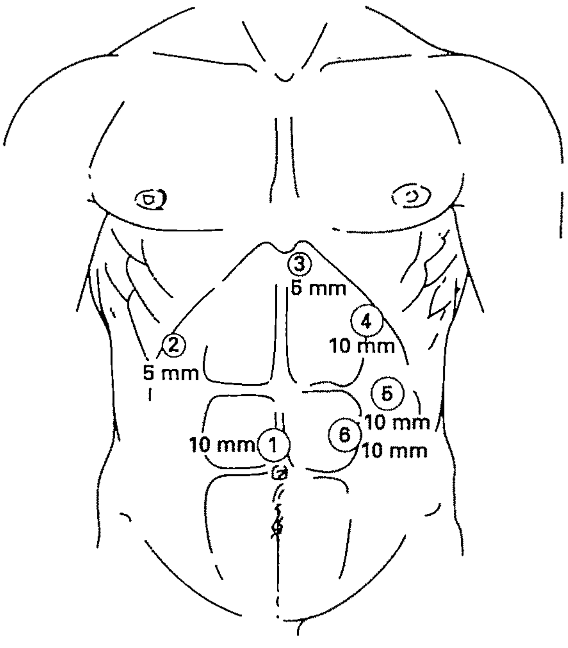

Fig. 1 Schematic representation of instrument penetration sites. 1 camera; 2 haemostatic forceps; 3 irrigation–suction system; 4 endoclip applicator, 5 scissor or grasping forceps; 6 ultrasonographic dissector. Operating surgeon uses ports 2 and 6, assistant surgeon ports 4 and 5, camera assistant ports 1 and 3

All patients underwent laparoscopic, non-anatomical liver resection; patient 2 also underwent laparoscopic cholecystectomy. The operation was performed with the patient in the supine position, with legs apart. The operating surgeon stood between the patient's legs, the assistant surgeon on the left side of the patient and the camera assistant on the right. Two videomonitors were positioned on either side of the anaesthetists, at the head of the table. After creation of the pneumoperitoneum at 13 mmHg, six trocars were introduced as illustrated in *Fig. 1*.

Following laparoscopy the hepatic ligaments were divided and Glisson's capsule incised using the diathermy hook approximately 2 cm from the lesion margin. An ultrasonographic dissector was used to dissect the parenchyma; the vascular and biliary pedicles were divided between resorbable clips. Haemostasis was completed by use of a diathermy spatula, argon beam diathermy and fibrin glue (Tissucol, Immunofrance S.A., Illkirch, France). Drainage was not used. The specimen was placed in a plastic endobag and extracted through an enlarged umbilical incision, slightly widened in cases 1 and 3. In patient 2 the specimen was removed via a McBurney incision.

Results

No blood transfusion was necessary; patients 1 and 3 were discharged on the fifth and patient 2 on the seventh day after operation without complication. In patient 1 histological examination showed undifferentiated adenocarcinoma cells, positive for CA 15-3 by immunoperoxidase testing. These were surrounded by a margin of normal hepatic parenchyma. Postoperative chemotherapy was given and the patient is alive without evidence of recurrence 17 months after operation. In patients 2 and 3 histological examination showed focal nodular hyperplasia.

Discussion

The advantages of laparoscopic surgery are established[4,5]; the absence of a painful incision allows early mobilization and shortens hospitalization. The magnification produced by the videocamera permits meticulous exploration of the peritoneal cavity and precise dissection of the hepatic vascular and biliary pedicles. Use of a laparoscopic ultrasonographic dissector preserves vascular and biliary structures and enhances the safety of videolaparoscopic hepatectomy.

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Short note

Intravenous cholangiography reduces the need for endoscopic retrograde cholangiopancreatography before laparoscopic cholecystectomy

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In the era of laparoscopic cholecystectomy, the management of patients with common bile duct (CBD) stones is controversial. Preoperative endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic stone extraction is currently the most popular option. Several studies have reported a 60–70 per cent incidence of negative ERCP before laparoscopic cholecystectomy in patients with risk factors for CBD stones[1,2]. This paper reports use of intravenous cholangiography (IVC) to try and reduce the requirement for ERCP in such patients.

Patients and methods

Some 231 patients underwent laparoscopic cholecystectomy for symptomatic gallstones. Liver function tests and biliary ultrasonography were performed routinely before surgery. IVC was undertaken in patients with risk factors for CBD stones unless they were jaundiced, had a history of dye allergy or a recent ERCP[3]. Risk factors for CBD stones included any abnormal liver function test, history of jaundice, pancreatitis or cholangitis, or extrahepatic biliary dilatation on ultrasonography. The decision to perform ERCP or IVC was determined individually.

Results

Sixty-three patients (38 women) had one or more risk factors for CBD stones. Twelve patients had ERCP and 47 had IVC as the primary investigation. Two patients with raised levels of liver enzymes inadvertently did not have preoperative IVC. Both subsequently had a normal operative cholangiogram. Two further patients with a minimal increase in alkaline phosphatase activity, considered to be at low risk for CBD stones, had no imaging performed because of a strong history of allergy.

Of twelve patients who underwent ERCP, CBD stones were identified and cleared in six. ERCP was negative in four patients and unsuccessful in two, one of whom had CBD stones demonstrated on operative cholangiography. Forty-seven patients had IVC, which revealed stones in 13. IVC gave false-positive results in two patients, in whom subsequent ERCP was negative. IVC was negative in 34 patients. One false-negative result was obtained in a patient whose operative cholangiogram and postoperative ERCP showed a single duct stone.

There were no major complications associated with IVC but two patients experienced mild cutaneous flushing.

During a mean(s.d.) follow-up of 20·3(10·5) months, no patient returned with evidence of retained CBD stones.

Discussion

Controversy continues over the management of CBD stones. The difficulty of dealing with such stones at laparoscopic cholecystectomy has led to a policy of preoperative ERCP in patients at risk of harbouring CBD stones. Risk factors for stones are neither sensitive nor specific, with the inevitable consequence of a high rate of negative ERCP. Modern IVC is accurate in detecting CBD stones[4]. Of 47 patients with risk factors in this study, 33 had a true-negative intravenous cholangiogram obviating the need for ERCP. Two false-positive cholangiograms resulted in unnecessary ERCP.

These results have lead the authors to advocate a policy of selective use of IVC in non-jaundiced patients with risk factors for CBD stones. This strategy will reduce the rate of negative ERCP. Facilities for ERCP are not immediately available to many surgeons who perform laparoscopic cholecystectomy and the performance of large numbers of negative procedures is a waste of resources. Conversely, IVC can be performed in all radiology departments and, in the authors' experience, is safe. IVC is useful to select patients at risk of CBD stones for ERCP before laparoscopic cholecystectomy.

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Adjuvant oral chemotherapy to prevent recurrence after curative resection for hepatocellular carcinoma

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Adjuvant oral chemotherapy was studied in 67 patients with stage II hepatocellular carcinoma who underwent curative resection between May 1988 and December 1990. Patients were stratified into two groups according to preoperative liver dysfunction: 55 had stage I disease (mild dysfunction) and 12 had stage II (moderate dysfunction). A randomized controlled study of postoperative oral administration of 1-hexylcarbamoyl-5-fluorouracil (HCFU) was conducted in each group. From October 1994 HCFU administration was suspended because of side-effects in nine patients with stage I liver dysfunction and in three with stage II dysfunction who had received the drug for more than 4 weeks. Cumulative survival and recurrence-free survival rates of patients with stage I disease in the treatment group were higher ($P = 0.08$ and $P = 0.04$ respectively) than those in the control group. However, in patients with stage II disease no significant difference was observed ($P = 0.77$ and $P = 1.0$ respectively). This study suggests that the potential benefits of HCFU on tumour recurrence should be weighed against the risks of adverse reactions in patients with mild liver dysfunction.

Postoperative survival rates in patients with hepatocellular carcinoma (HCC) who undergo complete excision of the tumour are improved by proper assessment of accompanying liver dysfunction and appropriate postoperative care. These longer surviving patients often have postoperative recurrence, either as metastatic or metachronous multicentric HCC[1–4]. Therefore, it is necessary to determine indications for oral adjuvant chemotherapy to prevent recurrence, particularly in patients with stage II HCC according to the Union Internacional Contra la Cancrum (UICC) classification who have a greater number of factors predisposing to recurrence, such as tumour size, vascular invasion or multiplicity (*Table 1*)[5], even after complete resection of tumours visible on imaging.

In patients with HCC, however, assessment of therapy to extend postoperative survival is not simple, since accompanying liver cirrhosis can induce dangerous side-effects when anticancer drugs are administered[6,7].

The oral anticancer drug 1-hexylcarbamoyl-5-fluorouracil (HCFU) is not metabolized by cytochrome P-450 in the liver, but is activated by natural non-enzymatic decomposition and by enzymatic oxidation in the liver[8]. Therefore, 5-fluorouracil levels in the blood can be maintained by a lower dose of HCFU, even in patients with impaired liver function[7]. To analyse the role of adjuvant chemotherapy after complete excision of the tumour, patients with stage II HCC were stratified prospectively according to clinical stage (*Table 2*)[9], as classified by the Liver Cancer Study Group of Japan to identify the degree of accompanying liver cirrhosis. In each stratified group, the effects of adjuvant chemotherapy on survival were assessed by a randomized controlled study.

Table 1 Definitions of stage II hepatocellular carcinoma according to the Union Internacional Contra la Cancrum classification[5] and of curative resection for these tumours according to the Liver Cancer Study Group of Japan[9]

Stage II hepatocellular carcinoma

1. A solitary tumour 2 cm or less in greatest dimension, with vascular invasion
2. Multiple tumours limited to one lobe, none more than 2 cm in greatest dimension, without vascular invasion
3. Solitary tumour more than 2 cm in greatest dimension, without vascular invasion
4. No regional lymph node metastasis detected

Curative resection for stage II hepatocellular carcinoma

1. Complete excision of a solitary tumour, less than 5 cm in diameter, with a tumour capsule and no vascular invasion to the first or second branches of the portal vein
2. For other stage II tumours, complete removal with a surgical margin from the tumour edge of more than 1 cm macroscopically

Table 2 Clinical stage of liver cirrhosis according to the Liver Cancer Study Group of Japan[9]

	Clinical stage		
	I	II	III
Ascites	None	Treatment effective	Treatment ineffective
Serum total bilirubin (mg/dl)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dl)	>3.5	3.0–3.5	<3.0
$ICGR_{15}$ (%)	<15	15–40	>40
Prothrombin activity (%)	>80	50–80	<50

The clinical stage of liver cirrhosis is determined by evaluating the patient's condition for each item; the patient is assigned to the most advanced stage with at least two items. These data do not necessarily correspond with the degree of advancement of the hepatocellular carcinoma. $ICGR_{15}$, indocyanine green retention rate at 15 min

Patients and methods

Between May 1988 and December 1990, 76 patients with UICC stage II HCC and no history of treatment within the previous

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3 months, who underwent curative resection, were registered to the Adjuvant Chemotherapy Study Group for Liver Cancer in Japan.

Curative resection for UICC stage II tumours was defined according to the general rule of the Liver Cancer Study Group of Japan[9] as indicated in *Table 1*. Patients were stratified into three groups (I–III) according to the degree of accompanying liver dysfunction[9].

Soon after surgery, stratified patients were registered with the central office by telephone, where postoperative treatment was chosen immediately by controlled randomization in each group: either no anticancer drug or oral intake of the anticancer drug 1-hexylcarbamoyl-5-fluorouracil (HCFU) (Carmofur; Mitsui Pharmaceutics, Tokyo, Japan). Administration of HCFU 200 mg twice daily was started 2–4 weeks after operation depending on the postoperative status. Administration was continued for as long as possible unless severe side-effects developed. No patient in any group received other medication such as antiviral agents or immunosuppressive drugs Patients who died within 1 month of operation, those who could not commence HCFU intake within 4 weeks of surgery and those who could not take the drug continuously for more than 4 weeks were treated as withdrawn cases. With respect to treatment for patients with an interruption of HCFU intake due to side-effects from HCFU; the following principles were decided before the start of the study: those who could not continue taking HCFU due to neuropathy[10] were not given HCFU again, while those who had disturbances in blood tests indicating, for example, bone marrow suppression or liver dysfunction, or symptoms such as frequent urination or exanthema, resumed use when blood test values returned to previous levels or symptoms disappeared. However, patients with a period of interruption of more than 2 months due to side-effects were not given HCFU again.

Recurrence was evaluated carefully on routine imaging examinations, at least once every 2 months with ultrasonography and once every 6 months with computed tomography. In some patients with suspected recurrence, the results of selective angiography, fine-needle biopsy or increased levels of tumour markers were also evaluated. Whenever recurrence or side-effects appeared, a report was made to the central office. Routine follow-up reports obliged each institution to present data on blood testing and the incidence of recurrence or side-effects twice a year. General meetings of the 26 institutions involved were also held twice yearly to examine these reports. Patients who stopped receiving HCFU for more than 2 months for any reason, including side-effects, or those who developed recurrence were considered as incomplete cases and subsequent treatment was decided according to each institution's policy. However, the status of these patients regarding recurrence and outcome had to be reported to the central office twice yearly, as for 'complete' cases.

In the stratified groups, with and without withdrawn cases, clinical characteristics of patients and factors relating to tumour proliferation were compared with the χ^2 test for sex, accompanying oesophageal varices, location of tumour, number of tumours, resected segments of the liver, growth type (expansive or infiltrative), tumour capsule formation, macroscopic tumour capsule infiltration, whether the surgical margin exceeded 1 cm from the tumour edge, portal invasion, Edmondson's grade[11] of the resected tumour, and macroscopic status of liver cirrhosis in the non-cancerous portion.

Cumulative recurrence-free survival rates, as well as cumulative survival rates in October 1994, were compared between the control and treated patients in each stratified group, with and without the withdrawn cases. Significance was determined by the generalized Wilcoxon test. All studies were performed after obtaining informed consent from patients and their families.

Results

Of the 76 registered patients with UICC stage II HCC, only one had clinical stage III liver dysfunction, whereas 61 (80 per cent) had clinical stage I and 14 (18 per cent) clinical stage II liver dysfunction (*Table 3*). In eight patients the surgical margin was less than 1 cm from the tumour edge; these patients were excluded from the study because the resection was non-curative (six with clinical stage I and two with stage II liver dysfunction). In the remaining .68 patients, HCFU administration did not follow the protocol in eight, who were withdrawn: one surgical death (clinical stage I), six (five with clinical stage I and one with stage II cirrhosis) who could not start within 4 weeks because of postoperative complications relating to liver dysfunction, and one (with clinical stage I) who took HCFU for less than 4 weeks and who had an interruption for more than 2 months because of liver dysfunction, possibly a side-effect of HCFU.

There were no significant differences in clinical features and factors relating to tumour proliferation between the control and treatment groups in patients with either stage I or II liver dysfunction. The surgical margin was 1 cm or more in all patients. There were no cases of hepatic vein invasion, bile duct invasion, peritoneal dissemination, lymph node metastasis or distant organ metastasis. Most tumours were solitary. Portal invasion was found in only one patient with clinical stage I dysfunction. Macroscopically the non-cancerous portions of the liver were cirrhotic in 36 (65 per cent) of 55 patients with clinical stage I and in ten of 12 with stage II dysfunction

As a side-effect of HCFU, neuropathy[10] was found in five patients, liver dysfunction in five, exanthema in four,

Table 3 Details of patients with stage II hepatocellular carcinoma entering the randomized controlled study of postoperative oral administration of 1-hexylcarbamoyl-5-fluorouracil

	Liver cirrhosis						
	Stage I		Stage II		Stage III		
	Control	HCFU	Control	HCFU	Control	HCFU	Total
Number registered*	31	30	7	7	0	1	76
Non-curative resection†	4	2	2	0	0	0	8
Number remaining within protocol	27	28	5	7			67
Number withdrawn‡	0	7	0	1			8
Overall no.§	27	21	5	6			59

HCFU, 1-hexylcarbamoyl-5-fluorouracil. *Patients registered at the central office as compatible with the protocol; †patients registered but did not undergo curative resection; ‡those in the treatment group who underwent curative resection but could not receive HCFU for more than 4 weeks because of postoperative liver dysfunction; §patients compatible with the protocol after exclusion of withdrawn patients leucopenia in one, frequent urination in one and diarrhoea in one. HCFU intake was suspended due to side-effects in nine of 21 patients with clinical stage I and in three of six with stage II cirrhosis, although these symptoms resolved within 2 months of suspension of the drug. The main side-effects necessitating suspension of therapy and the duration of HCFU intake in these patients are shown in *Table 4*. One patient with stage I dysfunction with frequent urination in the fifth week resumed HCFU intake 40 days later, after disappearance of the symptom. Another patient with stage I dysfunction stopped taking HCFU in the 41st month because of difficulty with oral administration following an accident.

During the observation period local recurrence or distant metastasis in patients with clinical stage I dysfunction was observed in 20 of 27 in the control group and in 15 of 28 (ten of 21 after exclusion of the withdrawn cases) in the treatment group; in patients with stage II dysfunction, three of five in the control group and seven of seven in the treatment group had recurrence (*Table 5*).

Details of 30 patients who died during the observation period are given in *Table 6*. Twenty-five patients died following recurrence, and five with no recurrence.

In patients with clinical stage I dysfunction, the cumulative survival rate was higher ($P = 0{\cdot}08$) in the treatment group than in the control group (*Fig. 1*). The result is clearer ($P = 0{\cdot}007$) after exclusion of withdrawn patients who could not start HCFU because of postoperative liver dysfunction. However, in patients with clinical stage II disease, no significant difference was observed ($P = 0{\cdot}77$ including withdrawn cases, $P = 0{\cdot}92$ without withdrawn patients). Similarly, in patients with stage I dysfunction, the recurrence-free survival rate of

Table 4 Patients who suspended 1-hexylcarbamoyl-5-fluorouracil intake because of side-effects

	Liver cirrhosis	
	Stage I	Stage II
Neuropathy	4 (2, 2·5, 6, 18)	1 (12)
Liver dysfunction	4* (3·5, 8, 9, 13)	1 (6)
Exanthema	1 (5)	
Diarrhoea		1 (7·5)

Values in parentheses are the duration of drug intake in months. *One withdrawn patient who was unable to take the drug for more than 4 weeks is not included

Table 5 Pattern of recurrence

	Liver cirrhosis			
	Stage I		Stage II	
	Control	HCFU	Control	HCFU
No recurrence	7	13 (11)	2	0 (0)
Local recurrence	17	12 (8)	3	7 (6)
Distant metastasis*	3	3 (2)	0	0 (0)
Total	27	28 (21)	5	7 (6)

Values in parentheses are the number remaining after the exclusion of withdrawn patients. *Includes patients with both local recurrence and distant metastasis. HCFU, 1-hexylcarbamoyl-5-fluorouracil

Table 6 Cause of death

	Liver cirrhosis			
	Stage I		Stage II	
	Control	HCFU	Control	HCFU
Recurrence				
Cancer death	10	5 (3)	1	4 (4)
Rupture of oesophageal varices	1	0 (0)	0	0 (0)
Liver failure	1	0 (0)	0	0 (0)
Cerebral thrombosis	0	0 (0)		1 (1)
Gastrointestinal bleeding	0	0 (0)	0	1 (1)
Other	0	1 (0)	0	0 (0)
No recurrence				
Liver failure	3	1 (0)	0	0 (0)
Brain injury	0	0 (0)	1	0 (0)
Total	15	7 (3)	2	6 (6)

Values in parentheses are the number remaining after exclusion of withdrawn patients. HCFU, 1-hexylcarbamoyl-5-fluorouracil

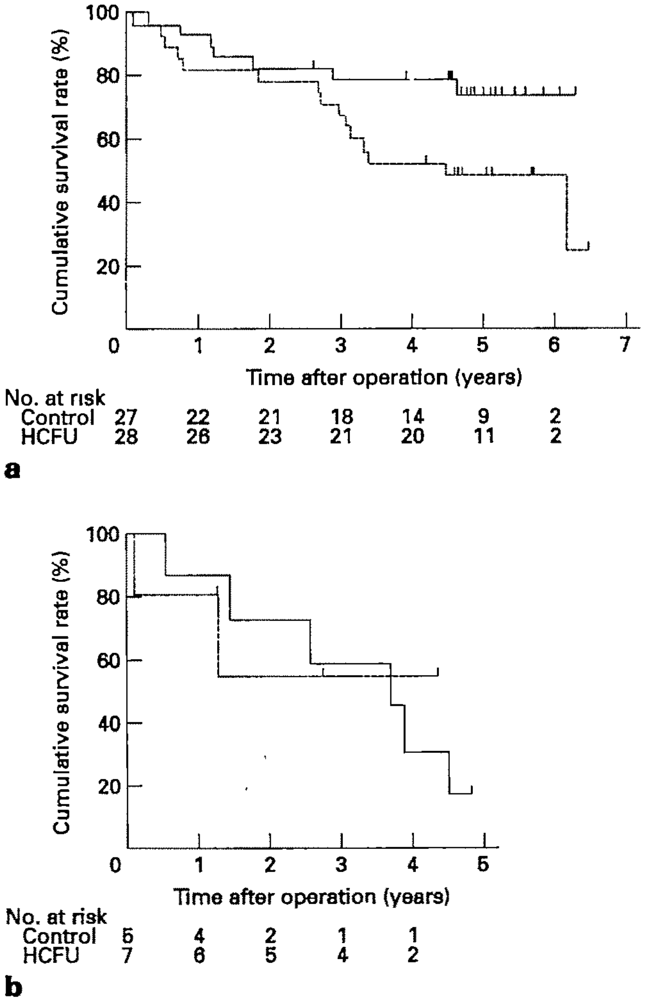

Fig. 1 Cumulative survival rates of patients with a stage I and b stage II liver cirrhosis. ----, Control; ———, treatment with 1-hexylcarbamoyl-5- fluorouracil (HCFU). a $P = 0{\cdot}08$, b $P = 0{\cdot}77$ (control *versus* HCFU, Wilcoxon test). Vertical bars indicate cut-off patients who were not dead as of October 1994

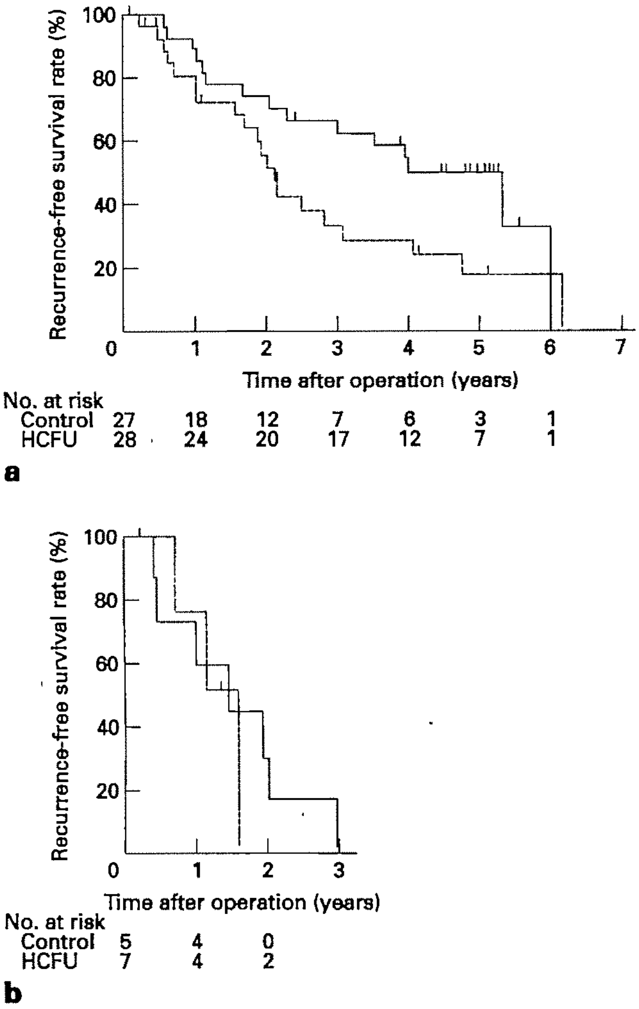

Fig. 2 Cumulative recurrence-free survival rates of patients with a stage I and b stage II liver cirrhosis. ----, Control; ———, treatment with 1-hexylcarbamoyl-5-fluorouracil (HCFU). a $P = 0{\cdot}04$, b $P = 1{\cdot}0$ (control *versus* HCFU, Wilcoxon test) Vertical bars indicate cut-off patients who were not dead as of October 1994

the treatment group was higher ($P = 0{\cdot}04$ including withdrawn cases, $P = 0{\cdot}003$ without withdrawn patients) than that of the control group, whereas no significant difference was observed in those with stage II dysfunction (*Fig. 2*).

Discussion

Recent improvements in the early diagnosis of small HCC lesions and procedures for liver resection have lengthened postoperative survival. However, frequent recurrence, even after complete excision of small tumours, indicates the necessity of analysing recurrence patterns[3] and evaluating protocols for adjuvant chemotherapy[6,7]. However, few randomized controlled studies have been carried out in patients with HCC, since anticancer drugs are sometimes more harmful to the host than to the cancer cells. In particular, more than 80 per cent of patients with hepatoma in Japan have accompanying liver cirrhosis[12] and the side-effects of anticancer drugs can be life threatening.

In the present study patients with UICC stage II HCC were prospectively stratified after curative resection by the extent of liver dysfunction. According to recent analyses of postoperative recurrence after complete excision of small hepatomas, recurrent tumours originate either from invisible minute tumour foci which were not identified by preoperative imaging or from metachronous multicentric HCC[3]. The present study indicates distinct differences in survival and recurrence-free survival rates in control and treated patients with stage I liver dysfunction, whereas there was no difference in those with stage II cirrhosis. These results suggest the influence of the anticancer drug in patients with liver dysfunction as well as a possible effect of HCFU in depressing the development of minute hepatomas.

Possibly HCFU either kills or prevents the growth of invisible minute tumour foci which were not identified by preoperative imaging, or inhibits the development of metachronous multicentric HCC, with fewer severe side-effects on the liver. It is probable that oral intake of anticancer agents induces a high portal concentration of the drugs, which then achieves tumoricidal effects on lesions in the precancerous stage. Patients with UICC stage II hepatoma and stage I liver dysfunction, could tolerate the surgical insult and survived longer with fewer side-effects from HCFU. However, those with stage III liver dysfunction, which indicates the decompensated stage of liver cirrhosis, were less able to undergo curative liver resection and seemed to be more vulnerable to anticancer drugs. Even in patients with stage II dysfunction, careful attention to early side-effects is required for this adjuvant chemotherapy. Despite the high frequency of side-effects, the potential benefits of HCFU on tumour recurrence should be weighed against the risks of adverse reactions in patients with liver cirrhosis.

In the present multi-institutional study, the small number of patients overall (59) with a mean of 2·3 inclusions per institution may have biased the results. Nevertheless, to control the accuracy of the study, each institution remained in close communication with the central office and biannual general meetings were held to maintain the same standard of treatment, particularly with regard to drug discontinuation due to side-effects and resumption of drug intake. The study showed, at least, that patients with clinical stage I dysfunction who received continuous HCFU intake for more than 4 weeks after operation had a higher recurrence-free survival rate.

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Laparoscopic common bile duct exploration: evolution of a new technique

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Laparoscopic exploration of the common bile duct (CBD) with a choledochoscope or a stone basket during laparoscopic cholecystectomy was attempted in 60 patients and was successful in 56. The cystic duct was used for entry to the CBD in 46 patients and in 14 a choledochotomy was performed. Of 51 patients with confirmed common duct stones, 38 had complete laparoscopic clearance (75 per cent). In 13 patients the duct was not cleared or was only partially cleared, of whom four went on to have clearance by postoperative percutaneous choledochoscopy down a cystic duct or T-tube track. Two patients with cystic duct tubes passed their remaining stones spontaneously. One patient had open exploration and six required endoscopic retrograde cholangiopancreatography. Of nine patients without stones, choledochoscopy was impossible in three patients whose cholangiogram was later considered to be normal. In five patients stones were excluded by choledochoscopy and in one patient laparoscopic choledochoscopy was undertaken to better define abnormal biliary anatomy; this helped to avoid major bile duct injury. Choledochoscopy was easier with the smaller 3·6-mm ureteroscope but stone removal was more difficult when the basket was too small for the stones, the cystic duct too small relative to stone size or the number of stones was too great. Successful stone clearance was proportional to the level of effort expended, and was limited by operating time and equipment.

The technique of laparoscopic cholecystectomy is now widely established and has brought with it a new perspective on the management of common bile duct (CBD) stones. When open cholecystectomy was common practice, common duct stones were usually removed by open CBD exploration. During the past decade increased use of choledochoscopy resulted in complete clearance of common duct stones in almost all patients[1]. Endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy could also be used to treat common duct stones either alone or combined with operation[2]. However, ERCP and sphincterotomy carries a significant failure rate, a morbidity rate of up to 15 per cent and mortality rate of about 1 per cent, and does not deal with cholelithiasis[3]. Often, therefore, it was reserved as the sole treatment only in the elderly and medically unfit.

With the advent of laparoscopic cholecystectomy, ERCP and endoscopic sphincterotomy has become the usual procedure for treating common duct stones because, unlike laparoscopic cholecystectomy, laparoscopic CBD exploration is not yet a widely practised technique. Moreover, cholecystectomy without cholangiography is commonly performed in the expectation that ERCP and sphincterotomy will be effective in dealing with unrecognized retained common duct stones. Other strategies include selective operative cholangiography with postoperative ERCP and sphincterotomy in those with CBD calculi. Alternatively, ERCP may be performed as a routine preoperative measure either in all patients with risk factors for choledocholithiasis, or selectively in those in whom stones have been demonstrated by other imaging techniques. With such reliance on ERCP, the procedures required to complete stone clearance are multiplied and new resources for ERCP will be required. Laparoscopic common duct exploration has the advantage of being a single procedure for the patient, but is not a widely practised technique.

Laparoscopic exploration of the CBD may be performed through the cystic duct or common duct using either fibreoptic instruments or radiologically guided wire baskets or balloons. Instrumentation may also be undertaken 'blind'. The laparoscopic approach to the common duct was developed initially by the transcystic route because of the ease of duct closure without recourse to suture as required in choledochotomy. Unfortunately it is sometimes difficult to pass instruments down the cystic duct. Because of the angle at which the cystic duct joins the common duct, the common hepatic duct and the intrahepatic ducts are relatively inaccessible. This is in contrast to the approach through the CBD. This latter approach has its advocates amongst laparoscopic surgeons because of ease of instrumentation, permitting the use of larger-calibre choledochoscopes and with them larger baskets. Additionally, the upper ducts are accessible for exploration. Where there is the facility for screening in the operating theatre, wire basket or balloon manipulation is performed in the same manner as by ERCP. Balloons may be used not only to dilate the cystic duct to permit instrumentation with a choledochoscope but also to dilate the ampulla of Vater. Calculi may be pulled or pushed with balloons. Choledochoscopy was increasingly used in open CBD exploration as the exploring instrument to achieve clearance of the duct rather than as a postexploratory check so it was natural for surgeons to use the same techniques during laparoscopic surgery. In this technique stone-grasping baskets are used to retrieve calculi. Traditionally at open surgery, the CBD was decompressed with a T tube until it was known that the bile was draining satisfactorily through the ampulla and there was no bile leak. Most series of laparoscopic common duct explorations through the cystic duct do not report the routine use of drainage of the common duct but most indicate the placement of a T tube if a choledochotomy was performed.

The authors' initial experience with laparoscopic CBD exploration using a variety of these techniques is described, and the technical requirements for success, and

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the role this procedure may have in the future of biliary surgery are discussed.

Patients and methods

Patients

From April 1991 to April 1995, 638 laparoscopic cholecystectomies were undertaken. Sixty patients (9·4 per cent) were selected for laparoscopic common duct exploration either on the basis of an abnormal operative cholangiogram or of an abnormal cholangiopancreatogram with failed sphincterotomy. Laparoscopic exploration of the CBD was indicated by the presence of a ductal filling defect on cholangiography, a dilated common duct, impaired flow into the duodenum or an incomplete view of the biliary system. Most of the operations were performed by one surgeon (R.W.M.). Thirty-six patients had risk factors for choledocholithiasis (history of jaundice, raised liver enzyme levels or pancreatitis) of whom 28 had common duct stones. There were 10 patients with confirmed stones who did not have any preoperative indicators of choledocholithiasis.

Technique

The gallbladder fundus was used for retraction to expose Calot's triangle. Cholangiography was attempted routinely with three still plate exposures. A 5-mm (Olympus CHF P10; Keymed, Southend-on-Sea, UK) or 3·6-mm (Olympus URF-P) choledochoscope (used later in the series) was introduced into the epigastric cannula. A 10–5-mm rubber-capped metal reducing sleeve was used to prevent damage to the choledochoscope casing. The cystic duct was entered through the incision used for cholangiography. The gallbladder was left *in situ* for the procedure and was used to maintain tension on the cystic duct. Control of the choledochoscope was achieved using the tip of the cannula for manipulation. This procedure was undertaken initially with separate endoscopic cameras projected on to separate video screens, but subsequently image mixing on one video screen facilitated simultaneous control of the laparoscopic and endoscopic procedures. When the cystic duct was entered the tip of the cannula was held close to the point of entry to prevent looping of the choledochoscope outside the duct (*Fig. 1*). The anatomy of the lower biliary tree was defined and filling defects seen on cholangiography were confirmed by inspection (*Fig. 2*). If gallstones were found in the common duct, removal was attempted under direct vision. A Dormia basket (1·2-mm Wilson–Cook urological stone basket for the 3·6-mm choledochoscope; 1·6-mm Keymed or Wilson–Cook (Letchworth, UK) stone basket for the 5-mm instrument) was introduced through the irrigation channel of the choledochoscope, the stones were grasped and withdrawn with the choledochoscope (*Fig. 3*). The procedure was repeated until all calculi were removed and the ampulla of Vater could be visualized (*Fig. 4*). It was frequently possible, with the 3·6-mm choledochoscope, to pass through the ampulla into the duodenum and on occasions stones were pushed or carried through with the basket as an alternative to withdrawal through the cystic duct. Duct clearance was confirmed by completion choledochoscopy.

Following transcystic choledochoscopy, the choledochoscope was removed and two clips were applied to the cystic duct stump. If stone clearance was not successful during laparoscopy, a 12-Fr tube drain was left in the cystic duct stump and secured with a ligature. The tube was left *in situ* for 6 weeks, by which time a mature track had formed. If stones persisted on repeat cholangiography, percutaneous choledochoscopic duct exploration was undertaken down the drain track[4].

In most patients exploration of the CBD was attempted initially through the cystic duct as the least invasive technique but choledochotomy was performed on 14 patients either after unsuccessful manipulation via the cystic duct or as the primary route of exploration if there were large or multiple stones. In this technique a small transverse incision was made in the CBD just

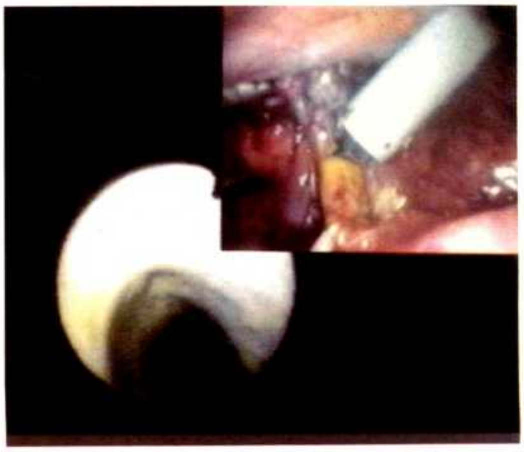

Fig. 1 The normal common bile duct visualized with the choledochoscope. In the inset picture the choledochoscope enters the biliary tree via the incision in the cystic duct used previously for the operative cholangiogram. The epigastric cannula is advanced close to the point of entry into the cystic duct to prevent the shaft of the choledochoscope looping within the abdominal cavity

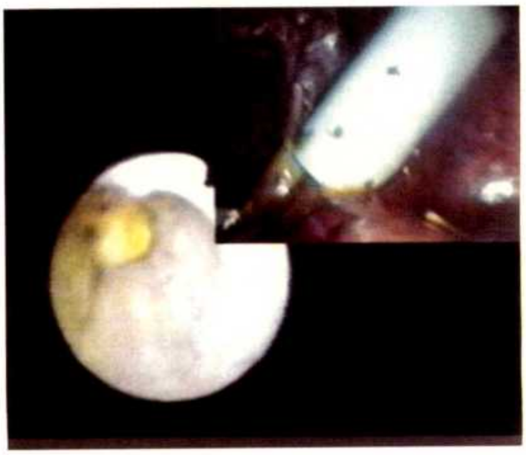

Fig. 2 A stone is visualized at the lower end of the common bile duct

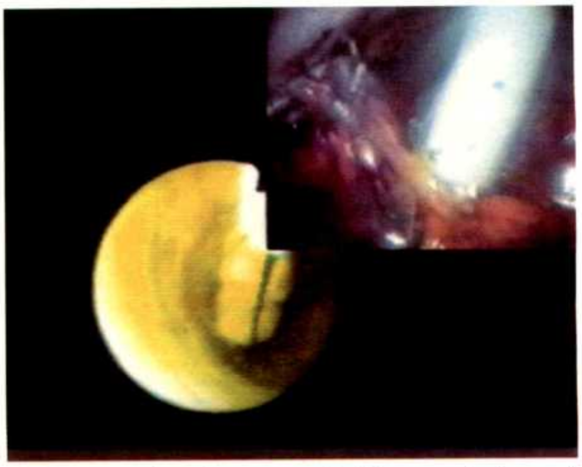

Fig. 3 Two stones have been grasped with a stone basket and are being withdrawn with the choledochoscope. The epigastric cannula is kept close to the entry point until the choledochoscope is about to exit from the cystic duct

below the apparent entry point of the cystic duct using hook scissors. At the end of the procedure the incision was closed using one or two interrupted 4/0 polyglactin sutures either over a T tube that was brought out through one of the cannula sites or else with primary common duct closure with subhepatic drainage.

Results

Cholangiographic and choledochoscopic findings

Fifty-one patients had common duct filling defects on cholangiography. In 14 the filling defects were multiple and small (less than 5 mm) and in 37 they were moderate (5–10 mm) or large (more than 10 mm). In eight cholangiograms there was impaired flow into the duodenum and a dilated CBD. In one cholangiogram there was no proximal duct filling. In this patient choledochoscopy was undertaken to clarify difficult anatomy (Mirizzi syndrome) and thereby major ductal injury was avoided.

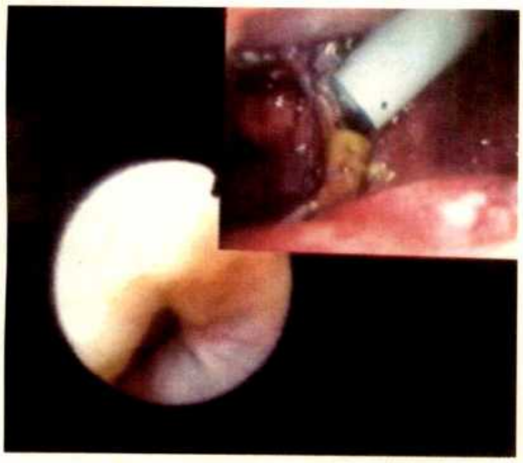

Fig. 4 The normal ampulla of Vater on completion choledochoscopy

Laparoscopic exploration of the CBD was attempted for suspected stones in 59 patients. Common duct calculi were confirmed in 51 patients; in one of these the procedure was converted to open exploration as a previous attempt at clearance by ERCP had failed. Of the remainder, five had no stones on choledochoscopy and in three the cystic duct was too narrow for the choledochoscope to pass. In retrospect cholangiograms from these three patients were probably normal. In two cases both the 5-mm and the 3·6-mm choledochoscopes were used; in the first patient difficult anatomy was being defined, and in the second severe inflammation and failed ERCP were indications for conversion to an open procedure so a prolonged attempt was not made. In 30 patients only the 5-mm choledochoscope was used either because it was the only one available (19 transcystic procedures; three failures not proceeding to choledochotomy) or out of preference in a choledochotomy (11 cases). In 24 patients only the 3·6-mm choledochoscope was used with only one failure of transcystic exploration but three of choledochotomy. In four cases small stones were removed using a stone basket blindly while awaiting sterilization of the choledochoscope and the ducts were clear on completion cholangiography.

Stone clearance

In 38 of 51 patients with confirmed stones (75 per cent), laparoscopic duct clearance was obtained. A further four had a complete clearance by choledochoscopy down a cystic duct tube track or a T tube track. Two patients passed a single residual stone spontaneously while waiting for their T tube track to mature. One patient went on to open common duct exploration (*Fig.* 5). The overall success of duct clearance without ERCP or open common

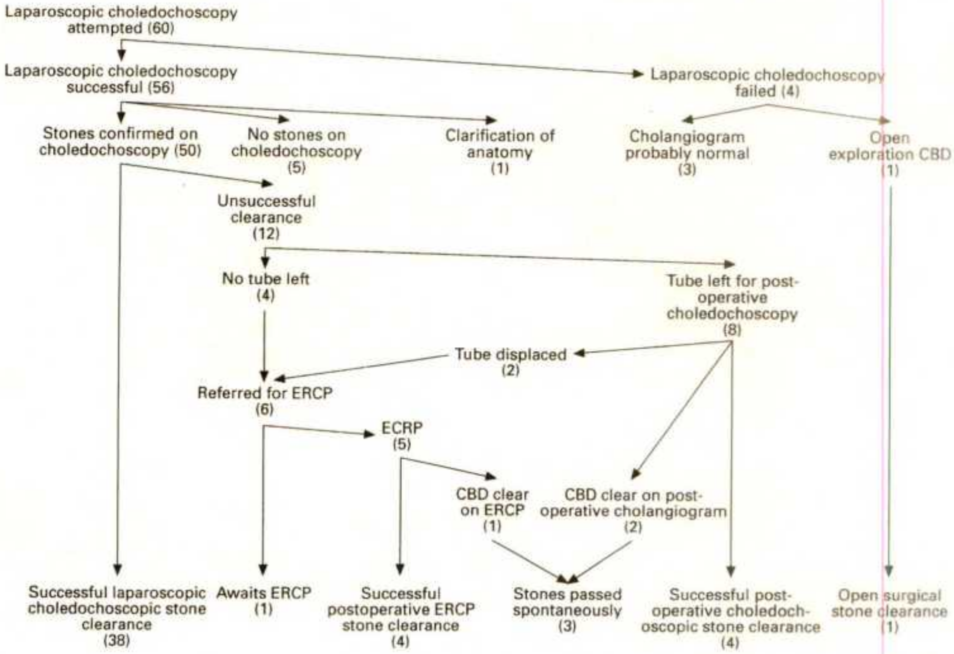
Laparoscopic choledochoscopy attempted (60)
Laparoscopic choledochoscopy successful (56)
Laparoscopic choledochoscopy failed (4)
Stones confirmed on choledochoscopy (50)
No stones on choledochoscopy (5)
Clarification of anatomy (1)
Cholangiogram probably normal (3)
Open exploration CBD (1)
Unsuccessful clearance (12)
No tube left (4)
Tube left for post-operative choledochoscopy (8)
Tube displaced (2)
Referred for ERCP (6)
ECRP (5)
CBD clear on ERCP (1)
CBD clear on post-operative cholangiogram (2)
Successful laparoscopic choledochoscopic stone clearance (38)
Awaits ERCP (1)
Successful postoperative ERCP stone clearance (4)
Stones passed spontaneously (3)
Successful post-operative choledochoscopic stone clearance (4)
Open surgical stone clearance (1)

Fig. 5 Results of 60 consecutive attempts at laparoscopic common bile duct (CBD) exploration. ERCP, endoscopic retrograde cholangiopancreatography

duct exploration therefore was 44 of 51 patients with confirmed stones (86 per cent).

In 38 successful laparoscopic procedures, a choledochoscope was inserted through the cystic duct in 23, the CBD was opened in 11 and a stone basket was passed blindly down the cystic duct in four. The success rate of choledochoscopy in the 51 patients with stones was 18 of 25 for the 5-mm choledochoscope and 20 of 26 for the 3·6-mm choledochoscope.

Six patients required postoperative ERCP because of failure to clear duct stones either during laparoscopy or postoperative choledochoscopy. Of these, four had sphincterotomy with stone retrieval, and one had no residual stones. One patient died from unrelated causes after 6 months without undergoing ERCP.

Reasons for failure of duct clearance during laparoscopy

The reasons for failure to clear the CBD were failure to grasp the stones, basket too small for the size of stone, crushing of the stone into multiple small fragments, poor views of the common duct, and tearing of the cystic duct preventing further access to the common duct. Of 12 patients in whom laparoscopic CBD clearance failed six had cystic duct tubes and two had T tubes placed at operation. Tube displacement prevented postoperative track choledochoscopy in two patients who had a cystic duct tube.

Costs and complications

The median time for laparoscopic cholecystectomy with common duct exploration was 150 (range 90–300) min compared with 80 (range 55–180) min for laparoscopic cholecystectomy. The median postoperative hospital stay was 3 (range 1–38) days.

Eight patients had complications. One patient in whom a cystic duct tube was placed had a bile leak; this was successfully managed by percutaneous drainage. One patient had prolonged drainage (not bile) from a subhepatic drain. Three patients had right hypochondrial pain or a pyrexia without ultrasonographic evidence of a leak but were nevertheless detained in hospital. One patient who had a partial duct clearance later presented with cholangitis while awaiting ERCP. One patient, admitted as an emergency, had a prolonged postoperative chest infection and therefore had a postoperative stay of 38 days. One patient had retention of urine.

Discussion

In this series laparoscopic stone clearance was obtained in 75 per cent of those with CBD calculi. Adding postoperative choledochoscopy, 84 per cent of patients had common duct clearance without ERCP. The results reflect the fact that this is a consecutive, unedited series of patients in whom laparoscopic common duct exploration was performed by surgeons developing and learning the technique. The rate of negative exploration was higher than that in the authors' previous series of open choledochoscopic CBD exploration[1] and is probably related to the development of laparoscopic cholangiography. An image intensifier that may have improved diagnostic accuracy was not available in this study. All these cases (i.e. those undergoing negative exploration) occurred in the first half of the series at which time there was undoubtedly a lower threshold for use of the choledochoscope. Nevertheless, transcystic common duct exploration with a choledochoscope or stone basket is of almost no consequence compared with open choledochotomy and was able to exclude common duct pathology in a minimally invasive manner.

Laparoscopic CBD exploration added approximately 1 h to standard operating time. Addition of balloon dilatation of the cystic duct or ampulla of Vater, or direct choledochotomy and placement of extra cannulas may have increased the success rate but with extra cost in time and equipment. The need to complete scheduled operating lists and other commitments limited operating time and sometimes precluded prolonged attempts at stone clearance.

Transcystic choledochoscopy was impossible in four patients, of whom three probably did not have stones on review of the cholangiograms. When stones have passed recently, the cystic duct may be intubated more easily. These patients came early in the series; with experience it was possible to judge that a narrow cystic duct was most unlikely to have passed a stone recently and this factor could be used to improve interpretation of the cholangiogram. In the fourth patient, readiness to perform a choledochotomy may have yielded success, as the difficulty with transcystic exploration arose because of concomitant cholecystitis. In the 12 patients in whom stones were not successfully removed, choledochotomy would have been the single most effective measure for dealing with the technical problems as basket size was limited with the transcystic route. The 3·6-mm choledochoscope is undoubtedly significantly easier to use for transcystic duct exploration than the 5-mm instrument but because it has a smaller irrigation channel, stone manipulation is less easy. The stone basket was sometimes inadequate for the size of stone. The authors found the lantern-shaped basket was better than the twisted spiral (Dormia) shape. However, with larger cystic ducts or after dilatation of the cystic duct or with choledochotomy, the 5-mm choledochoscope can be used and a bigger basket can be employed. Failure to grasp the stones occurs partly because the basket is too small but also because the inferior part of the common duct tapers and impaction of stones here prevents the basket from opening fully beyond the stone for subsequent withdrawal – a manoeuvre that is necessary to trap stones. Usually it is possible to disimpact stones with the closed basket to allow retrieval. Dilatation of the ampulla would facilitate this procedure.

A major factor in the additional operating time is the need to prepare the choledochoscope. In most of the present patients, stones were only identified during the operation. At the outset of this series the choledochoscope was prepared only when the indication for its use was apparent. Current practice is to have the choledochoscope prepared before laparoscopic cholecystectomy where there are risk factors for choledocholithiasis, but to wait for its preparation if common duct calculi are not anticipated. The use of the cystic duct tube drain with the aim of postoperative tube track choledochoscopy or radiological basket retrieval is an important way to save time during laparoscopy particularly when lack of time is the limiting factor in clearing a duct of stones. In this series, judgement that the common duct may well become obstructed by a stone was the main reason for providing drainage. Because of previous experience with T-tube track choledochoscopy it was a logical step to do the same after incomplete laparoscopic exploration of the CBD[4]. The relief of obstruction aided disimpaction of stones making postoperative track exploration easier and it seems possible that decompression may have contributed to the spontaneous passage of stones in two patients. A disadvantage of this procedure is that the patient has to keep a tube in place for 6 weeks in order to form a track. ERCP as an alternative was difficult to obtain promptly in this centre.

A number of series of laparoscopic CBD explorations has been reported and there are in addition several single-case reports[5-8]. A high success rate is reported and measures additional to or facilitating transcystic exploration are advocated. Blind or fluoroscopic procedures include the use of Segura and other stone baskets introduced directly into the biliary tree, dilating balloons applied to the cystic duct or ampulla of Vater, and Fogarty catheters to retrieve stones. The availability of an image intensifier in the operating theatre with the facility for freeze-frame image storage is essential for these techniques. The ampulla of Vater may be dilated with a biliary balloon catheter and any stones in the common duct may then be pushed into the duodenum using a half-inflated balloon. Radiological techniques have the advantage of providing full imaging of the biliary tract throughout the procedure, require less coordination with the laparoscopic view and baskets are more easily passed through the cystic duct. By contrast the clear view from endoscopic inspection is an advantage to ensuring complete clearance, but is more difficult to coordinate with the laparoscopic view. Most authors claim a success rate in the order of 90 per cent and we believe that such results are realistic with experience. Stone clearance at operation in the last ten cases of the present series was 100 per cent.

The cost of equipment is high but compares favourably with that of typical endoscopic equipment as may be used in ERCP. The 3·6-mm choledochoscope costs about £9000 and the 5-mm choledochoscope about £10 000. The former is the preferred instrument. An extra camera system costs £7000 and the digital mixer used to combine images costs about £1000. The stone baskets cost £90 each but are reusable. Extra operating time is expensive but in this series operating time was increased by the extra time required to prepare equipment. These extra costs have to be balanced against the advantage of a single procedure and short hospital stay.

For many surgeons ERCP is regarded as the least invasive method for the removal of common duct stones. It can be performed without anaesthetic and repeatedly and therefore has some advantages over laparoscopic CBD exploration. Additionally, sphincterotomy or insertion of a stent with sphincterotomy is an option when stone extraction fails[9]. There are potential disadvantages with the endoscopic approach to the common duct, and before comparisons of these approaches are made it must be remembered that patients referred for ERCP tend to have different characteristics to those having cholecystectomy[3]. Laparoscopic cholecystectomy adds a new contingency to the argument as this procedure has a proven safety record[5]. Laparoscopic exploration of the CBD has the advantage of incorporating two procedures in one operation and in due course may well become routine practice for biliary surgeons undertaking laparoscopic cholecystectomy in the same way as open exploration of the common duct was undertaken at the time of open cholecystectomy. The scarce availability of facilities for ERCP will mean the over-reliance on this technique to treat common duct stones as an adjunct to laparoscopic cholecystectomy will require a vast expansion of ERCP services. Preoperative ERCP in patients with abnormal liver function tests, a dilated common duct on ultrasonography, or a history of transient jaundice will prove to be normal in 50 per cent because these factors have poor predictive value for choledocholithiasis[10]. Reliance on postoperative ERCP will on occasions be unsuccessful because of technical difficulties such as duodenal diverticula. It is also important to remember that the mortality rate of ERCP in the best hands is in the order of 1 per cent[11] which is acceptable in the context of an elderly unfit patient in whom open CBD exploration may well carry a higher risk of death. However major complications of ERCP occur indiscriminately and its widespread use in younger patients (in whom either open or laparoscopic exploration of the CBD does not increase the mortality rate of simple cholecystectomy (about 0·3 per cent)[12]) will increase the overall risks of treatment of common duct stones.

The technical difficulties associated with laparoscopic CBD exploration will be overcome with suitable equipment and increased expertise. If this procedure is to be the primary treatment of common duct stones in patients with cholelithiasis, constant availability in the operating theatre of additional equipment is necessary, and time must be allowed. Perhaps fewer surgeons should do laparoscopic cholecystectomy to permit those surgeons to gain experience and to maintain expertise in laparoscopic exploration of the CBD. In the present series one surgeon was present in all cases, performing most operations and thus improved the success rate. There was about one laparoscopic CBD exploration performed per month; this is probably sufficient experience to maintain operative expertise. The current pre-eminence of ERCP in the context of laparoscopic cholecystectomy practised by a large pool of surgeons, however, may mean that laparoscopic exploration of the common duct will remain the province of the enthusiast or of centres with a keen interest in laparoscopy.

Widespread use of choledochoscopy at open cholecystectomy during the past decade resulted in complete clearance of the common duct at the time of surgery and it is likely that increasing use of choledochoscopy in this decade at the time of laparoscopic cholecystectomy will result in similarly complete clearance of the common duct at the time of operation. Biliary endoscopy at the time of operation rather than before or afterwards may prove to be in the patient's best interests[13].

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Announcement

Association of Gastrointestinal Surgeons of Great Britain and Ireland

This new Association will be formed under the umbrella of the Association of Surgeons of Great Britain and Ireland (ASGBI) and at the request of many of the Fellows of that Association. It will embrace the science and practice of surgery of the oesophagus, stomach, duodenum, jejunoileum, liver, gallbladder, biliary tree, pancreas, portal vein and spleen. As general surgery in Britain ramifies into groupings such as vascular, breast, endocrine, transplant surgery and coloproctology, so each is developing its own professional organization. The new Association of Gastrointestinal Surgeons is created to represent those with either an oesophagogastric or an HPB (hepatopancreatobiliary) interest, since it is anticipated that these two disciplines will remain closely linked for the foreseeable future. The Association will provide a structure for education and training, clinical developments and research into some of the most challenging diseases that confront surgeons today. Support, both practical and conceptual, has been offered by the Royal Colleges of Surgeons and the ASGBI, as well as by the leading experts in the field.

A Steering Group was established in 1995 to help bring the Association of Gastrointestinal Surgeons into being, to prepare a draft constitution and to arrange an inaugural meeting for more detailed discussion of aims and activities. This meeting will take place during the Annual Meeting of the ASGBI in Glasgow on the morning of Thursday 23rd May 1996, with the following title and programme. We urge all those with an interest in the specialty to attend.

Gastrointestinal Surgery: Junctional Zones
10.30–12.15 hrs, 23 May 1996, Glasgow, UK

1 Scientific Update	
Zenker's diverticulum and the cricopharyngeus	T. N. Walsh
Splenectomy in the operative treatment of gastric cancer	D. Johnston
Papillary stenosis	R. C. G. Russell
Re-resection for hepatic metastases	M. Rees
2 Birth of the Association: live or still?	
Rationale and draft constitution	Steering Group

W. H. Allum
J. Bancewicz
G. Glazer
A. Watson
R. C. N. Williamson

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Short note

Peritoneal and systemic cytokine response to laparotomy

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Cytokines are polypeptides produced mainly by activated leucocytes in response to infection and injury, including surgical trauma. Several reports have described the systemic cytokine response to a surgical operation, some of them in a sequential way[1,2]. This study was designed to determine the peritoneal and systemic cytokine response to elective abdominal surgery during the first 72 h after operation.

Patients and methods

Patients

Patients were divided into two groups: those ($n = 6$) undergoing elective laparotomy for non-inflammatory disease (four colectomies, one gastrectomy, and one small bowel resection) (group 1); and those ($n = 6$) having elective pancreatic surgery (five pancreatoduodenectomies, one bypass) (group 2).

The study was approved by the Ethical Committee of the Royal Postgraduate Medical School, and all patients gave informed consent.

Samples

Peritoneal fluid was sampled through abdominal silastic drains (groups 1 and 2) and venous blood was taken from a central line (group 2). All samples were centrifuged at 2500*g* for 10 min at 4°C and the supernatant was stored at − 80°C until assay.

Cytokine assays

Interleukin 1β (IL-1β) (Cistron Biotechnology; Pine Brook, New Jersey, USA), interleukin 6 (IL-6) (Eurogenetics, Tessenderlo, Belgium) and tumour necrosis factor α (TNFα) (T Cell Diagnostics, Teddington, UK) were measured in plasma and peritoneal fluid using enzyme-linked immunosorbent 'sandwich' assays. The minimum detectable concentrations were 20 pg/ml for IL-1β, 5 pg/ml for IL-6 and 1·5 pg/ml for TNFα.

Results

Maximal median cytokine concentrations observed in the peritoneal fluid of patients in group 1 were: TNFα 272 (range less than 10–4300) pg/ml at 3 h after operation; IL-1β 154 (range 77–261) pg/ml at 3 h; and IL-6 241 (range 144–346) ng/ml at 5 h.

The peritoneal cytokine concentrations of patients in group 2 are shown in *Fig. 1*. In plasma, IL-1β and TNFα were undetectable (less than 20 pg/ml and less than 1·5 pg/ml, respectively) at all time points. The mean(s.e.m.)

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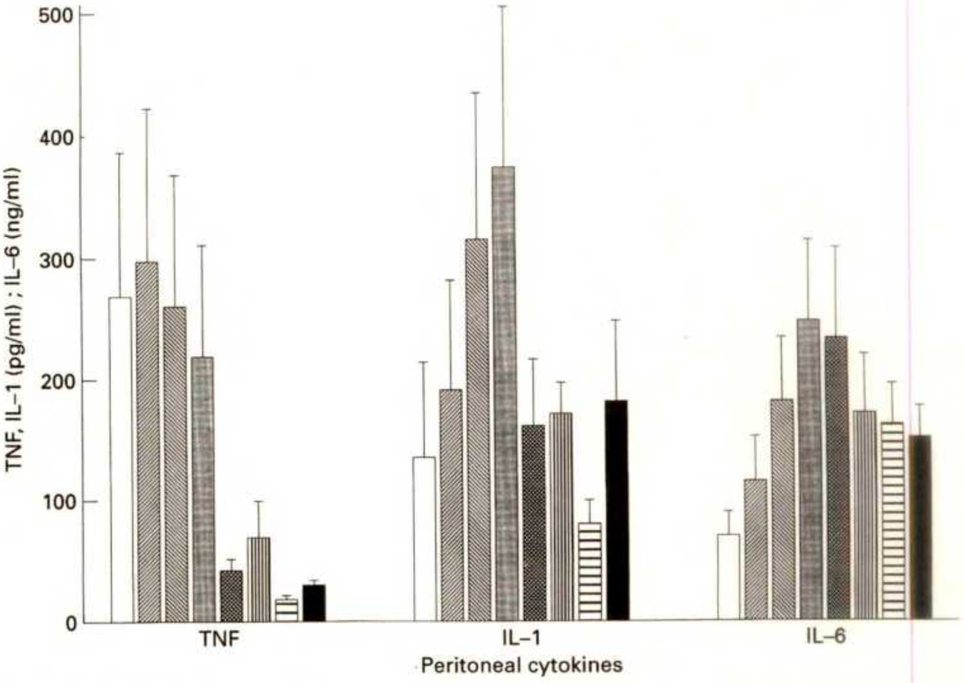

Fig. 1 Mean(s.e.m.) concentrations of tumour necrosis factor (TNF), interleukin-1(IL-1)β and IL-6 observed in peritoneal fluid during the first 72 h after operation. □, 6 h; ▨, 8 h; ▧, 10 h; ▩, 12 h; ▦, 24 h; ▥, 36 h; ▤, 48 h; ■, 72 h

preoperative plasma concentration of IL-6 was 0·03(0·01) ng/ml and the maximum value after operation was 0·84(0·55) ng/ml at 8 h.

Discussion

Several authors have reported increased plasma concentrations of IL-6 with low or undetectable plasma levels of TNFα and IL-1β after surgical operation[2,3]. Few reports, however, have addressed the cytokine response of the peritoneum[4]. In the present study a sequential, high-concentration peritoneal cytokine response to laparotomy was detected. The finding of much higher cytokine concentrations in peritoneal fluid than in plasma suggests that the postoperative cytokine response may originate largely from the peritoneal cavity. The systemic cytokine response may be simply an indirect reflection of this local response. The differences observed between plasma and intraperitoneal cytokine concentrations may be explained by incomplete absorption and rapid degradation of peritoneal cytokines and by their dilution in plasma. Cytokines absorbed into the portal circulation will be rapidly degraded by the liver. A local cytokine response produces several inflammatory changes, including stimulation of mesothelial cells[2]. This in turn can induce chemotaxis of neutrophils, further production of cytokines and alterations in fibrinolytic activity[5]. Peritoneal cytokines absorbed into the portal and systemic bloodstream may also stimulate the production of acute-phase proteins by hepatocytes.

Acknowledgements

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Serum concentrations of inflammatory mediators related to organ failure in patients with acute pancreatitis

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Leucocyte activation and proinflammatory cytokine release (tumour necrosis factor (TNF) and interleukin 6 (IL-6)) are thought to contribute to the induction of a systemic inflammatory response, an acute-phase response and multiple organ failure in patients with acute pancreatitis. The serum concentration of TNF, soluble TNF receptors (sTNFR$_{55}$ and sTNFR$_{75}$), IL-6 and C-reative protein (CRP) in 58 patients with acute pancreatitis was assessed during the first 2 days of admission. Thirty patients had mild disease and 28 severe disease, of whom 18 developed local pancreatic complications alone (Atlanta classification) and ten developed organ failure (a Goris score of 1 or more). TNF was detected in only 17 patients on the first day of admission, while soluble TNF receptors were detected in all patients and IL-6 in 34. On the first and second days of admission there was a progressive and significant ($P<0\cdot03$) increase in the median concentration of sTNFR$_{55}$, sTNFR$_{75}$ and IL-6 in patients eventually classified into those with mild disease, a local pancreatic complication alone, or organ failure. This pattern was also evident in CRP levels from the second but not the first day of admission. These findings suggest that proinflammatory cytokines or their soluble receptors may be more accurate early predictors of outcome than CRP. Moreover, markers of inflammation in the sera of patients with acute pancreatitis are highest in those who subsequently develop organ failure.

Acute pancreatitis remains a common and potentially fatal disease in which some patients develop extensive pancreatic inflammation and necrosis, a systemic inflammatory response and multiple organ failure[1]. It has been proposed that the systemic sequelae of pancreatitis arise from excessive leucocyte activation with the release of secondary mediators such as proinflammatory cytokines, including tumour necrosis factor (TNF) and interleukin (IL) 6[2]. The central role of TNF (a potent cytokine produced mainly by activated macrophages) in orchestrating aspects of the early inflammatory response in sepsis is well established[3]. Increased levels of TNF have been documented in the serum of some groups of patients with sepsis[4] and after exposure to endotoxin[5]. However, TNF is often undetectable in the sera of patients with acute pancreatitis, even those with severe disease[6,7]. This may be because of the short half-life of TNF, binding of TNF to other proteins, or difficulties with the various methods of measuring TNF in serum. Alternatively, it may be that TNF is not produced in patients with acute pancreatitis or is mainly produced in the tissues and only occasionally spills over into the circulation.

The paracrine and endocrine actions of TNF are exerted by interaction with membrane-bound TNF receptors on the surface of target cells[8]. It appears that after exposure to substances such as bacterial endotoxin (and indeed TNF itself), such target cells downregulate their responsiveness to TNF by shedding the receptor into the circulation[9]. Two such soluble receptors have been identified; a 55-kDa (sTNFR$_{55}$) and a 75-kDa (sTNFR$_{75}$) fragment[10]. The release of these soluble receptors (which have a longer half-life in serum than TNF itself) appears to reflect the degree of TNF-induced inflammation[11]. Thus, although TNF may be undetectable in blood, the presence of such soluble TNF receptors may be a useful index of TNF activity.

Other cytokines involved in the inflammatory cascade, such as IL-6, are more often detected in the sera of patients with acute pancreatitis[12–14]. Both the serum concentration of IL-6 on admission and the peak level of IL-6 have some correlation with the severity of the disease[12–14]. One of the many actions of IL-6 is to induce the production of hepatic acute-phase proteins, such as C-reactive protein (CRP). The serum concentration of CRP is also increased in patients with acute pancreatitis and correlates with the severity of the disease[15–17]. The rise in serum CRP concentration lags behind the peak in serum IL-6 concentration by some 24–48 h[18] and this has been interpreted by some investigators to indicate a cause and effect relationship.

It has been proposed that a prolonged or excessive inflammatory response may be one of the mechanisms whereby patients develop multiple organ failure[19,20]. The major causes of death in acute pancreatitis stem from either local peripancreatic complications or multiple organ failure, or a combination of the two. In the present study, the systemic inflammatory response as measured by markers of inflammation (TNF, sTNFR$_{55}$, sTNFR$_{75}$, IL-6 and CRP) in the serum of patients with acute pancreatitis have been investigated and related to the development of local complications and organ failure

Patients and methods

Patients with acute pancreatitis admitted to the Royal Infirmary, Edinburgh were studied. The diagnosis of acute pancreatitis was based on the presence of appropriate clinical or radiographic evidence accompanied by a serum amylase concentration greater than 1000 units/l (Phadebas; Pharmacia Diagnostics, Uppsala, Sweden; normal range 70–300 units/l). The clinical course of the patients was followed prospectively, allowing retrospective categorization of patients into those with mild or severe disease based on the Atlanta classification[21]. Twenty-eight patients with severe disease represented a consecutive series over a 16-month period. Thirty of 78 patients with mild disease admitted over the same time period were randomly selected for comparison.

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Patients with severe disease were further subcategorized into those with local pancreatic complications alone ($n = 18$) and those with organ failure (a Goris score[22] of 1 or more; $n = 10$). Six patients with organ failure died during the index admission. Gallstones were suspected as the aetiology in 26 patients, alcohol in 18 and the presence of pancreatic cancer in one. Pancreatitis complicated endoscopic retrograde cholangiography in two patients and the aetiology was not identified in 11. Venous blood was sampled on the first and second day of admission and the serum stored at −70°C until subsequent batch analysis for TNF, $sTNFR_{55}$, $sTNFR_{75}$, IL-6 and CRP concentration by indirect enzyme-linked immunosorbant assay (ELISA).

Assay of cytokines and C-reactive protein

TNF was measured with an ELISA using a murine monoclonal antihuman TNF antibody and peroxidase-conjugated Fab fragments of a murine monoclonal antihuman TNF antibody (Boehringer Mannheim, Lewes, UK). A standard curve was constructed with recombinant human TNF (British Biotechnology, Abingdon, UK) and calibrated with an international standard (NIBSC, Potters Bar, UK). The lower limit of detection of the assay was 15 pg/ml.

Serum $sTNFR_{55}$ and $sTNFR_{75}$ were detected by ELISA, with monoclonal and polyclonal anti-$sTNFR_{55}$ and anti-$sTNFR_{75}$ antibodies. Purified $sTNFR_{55}$ and $sTNFR_{75}$ were used to construct standard curves. The lower limit of detection of the assay was 150 pg/ml for both receptors.

The ELISA for IL-6 used a murine monoclonal antihuman IL-6 antibody (Boehringer Mannheim) as the capture antibody and a goat polyclonal (non-enzyme labelled) antihuman IL-6 (R&D Systems, Oxford, UK) followed by a peroxidase-conjugated sheep antigoat immunoglobulin G antibody (Sigma Immunochemicals, Poole, UK) to detect bound IL-6. A standard curve was constructed with recombinant human IL-6 (British Biotechnology) and calibrated with an international standard (NIBSC). The lower limit of detection of the assay was 30 pg/ml.

CRP was detected by sandwich ELISA, with rabbit antihuman CRP and peroxidase-conjugated rabbit antihuman CRP (DAKO, High Wycombe, UK). A standard curve was constructed with a human serum CRP calibrator (DAKO). The lower limit of detection of the assay was 1 mg/l.

Statistical analysis

Results are presented as the median (interquartile range). Initial comparison among patients with mild disease, a local pancreatic complication alone and organ failure was performed using the Kruskal–Wallis test. Thereafter, Mann–Whitney U tests were applied to compare differences between any two groups; significance was assumed when $P<0\cdot05$. Where levels of the cytokine being measured were below the limit of detection of the assay, the minimum detection concentration was assigned to the sample and statistical analysis was performed using this convention.

Results

None of the 30 patients with mild disease developed significant complications. In contrast, 18 of 28 with severe pancreatitis developed local complications alone, while the remaining ten developed failure of one or more organ systems, with or without an accompanying local pancreatic complication. There was no significant difference in the age ($P=0\cdot29$) or sex ratio ($P=0\cdot57$) between those with mild pancreatitis and those with severe pancreatitis.

Serum concentrations of TNF were below the level of detection in 41 of 58 patients on the first day of admission (29 of 30 with mild disease, eight of 18 who developed a local pancreatic complication and four of ten who developed organ failure) and 50 of 58 on the second day (all with mild disease, 16 of 18 who developed a local pancreatic complication and four of ten who developed organ failure). On the first day of admission, the median serum concentration of TNF was greater in patients who developed organ failure ($P<0\cdot001$) and in those who developed a local pancreatic complication ($P<0\cdot001$) than in those with mild disease (*Table 1*). There was no significant difference between patients who developed organ failure and those who developed a local pancreatic complication alone ($P=0\cdot34$). On the second day of admission, the median serum concentration of TNF was greater in patients who developed organ failure than in those who developed a local pancreatic complication ($P<0\cdot006$) and in those who had mild disease ($P<0\cdot006$) (*Table 1*). There was no significant difference between patients who developed a local pancreatic complication alone and those who had mild disease ($P=0\cdot07$).

Serum $sTNFR_{55}$ and $sTNFR_{75}$ were detectable in the 58 patients. On both days 1 and 2 of admission, the median serum concentration of $sTNFR_{55}$ was greater in patients who developed organ failure than in those who developed a local pancreatic complication ($P<0\cdot003$). In both

Table 1 Concentration of serum tumour necrosis factor (TNF) and serum C-reactive protein (CRP) in patients with acute pancreatitis on the first and second day of admission

	Mild disease ($n=30$)	Pancreatic complication alone ($n=18$)	Organ failure ($n=10$)
Serum TNF (pg/ml)			
Day 1	15·0 (15·0–15·0)	17·8 (15·0–23·8)	22·6 (15·0–75·1)
Day 2	15·0 (15·0–15·0)	15·0 (15·0–15·0)	21·1 (15·0–51·4)
Serum CRP (mg/l)			
Day 1	31·4 (10·0–61·5)	11·6 (7·8–36·5)	36·0 (14·9–58·9)
Day 2	36·1 (22·8–84·4)	33·0 (19·7–121·1)	99·9 (79·4–136·2)

Values are median (interquartile range)

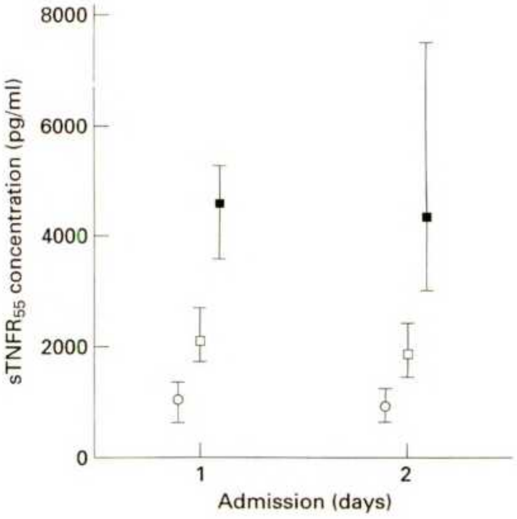

Fig. 1 Median serum concentration of soluble tumour necrosis factor receptor (55 kDa) ($sTNFR_{55}$) on the first and second day of admission in patients with acute pancreatitis categorized by mild disease (○; $n = 30$), local pancreatic complication alone (□; $n = 18$) and organ failure (■; $n = 10$). Interquartile range represented by the error bars

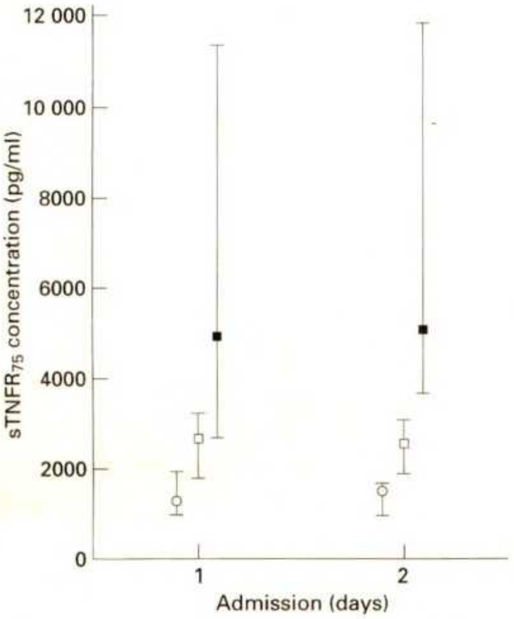

Fig. 2 Median serum concentration of soluble tumour necrosis factor receptor (75 kDa) ($sTNFR_{75}$) on the first and second day of admission in patients with acute pancreatitis categorized by mild disease (○; $n = 30$), local pancreatic complication alone (□; $n = 18$) and organ failure (■; $n = 10$). Interquartile range represented by the error bars

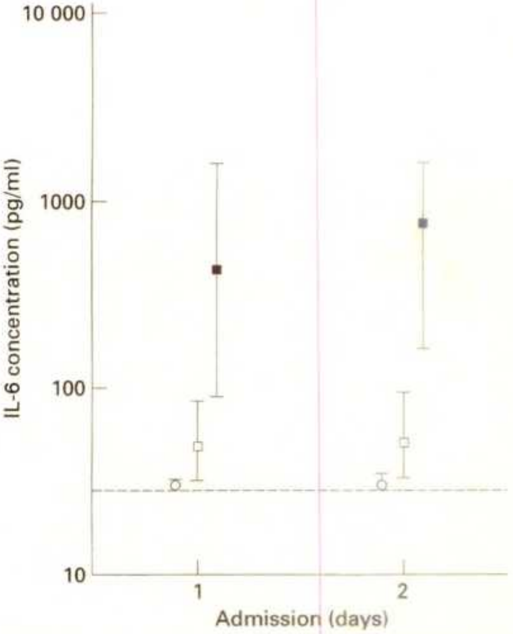

Fig. 3 Median serum concentration of interleukin (IL) 6 on the first and second day of admission in patients with acute pancreatitis categorized by mild disease (○; $n = 30$), local pancreatic complication alone (□; $n = 18$) and organ failure (■; $n = 10$). Interquartile range represented by the error bars. Lower limit of detection of the assay represented by the dashed line

groups with severe disease, the median serum concentration of $sTNFR_{55}$ was greater than that in patients who had mild disease ($P < 0{\cdot}001$ in both cases) (*Fig. 1*). Serum concentrations of $sTNFR_{75}$ showed a similar distribution among the three groups to that found for the $sTNF_{55}$ receptor (*Fig. 2*).

Serum concentrations of IL-6 were below the level of detection in 24 of 58 patients on the first day of admission (20 of 30 with mild disease, three of 18 who developed a local pancreatic complication and one of ten who developed organ failure) and in 23 of 58 on the second day (19 of 30 with mild disease and four of 18 who developed a local pancreatic complication). On both days 1 and 2 of admission, the median serum concentration of IL-6 was greater in patients who developed organ failure than in those who developed a local pancreatic complication alone ($P < 0{\cdot}03$), which in turn was greater than in those with mild disease ($P < 0{\cdot}001$) (*Fig. 3*).

CRP was detectable in the serum of all patients. On the first day of admission, there was no significant difference in the median serum levels of CRP among patients who developed organ failure or a local pancreatic complication and those who had mild disease ($P = 0{\cdot}15$) (*Table 1*). By the second day of admission, the median serum concentration of CRP was greater in patients who developed organ failure than in those who developed a local pancreatic complication ($P = 0{\cdot}02$) or those who had mild disease alone ($P = 0{\cdot}003$) (*Table 1*). However, the median serum CRP level in patients who developed a local pancreatic complication was not significantly different from that in those with mild disease ($P = 0{\cdot}80$) (*Table 1*).

Discussion

The present study demonstrates that during the first 2 days of admission, concentrations of markers of inflammation in the sera of patients with acute pancreatitis are highest in those who subsequently develop organ failure.

TNF has been implicated as a key mediator in the development of multiple organ failure[20,23]. In the present study, however (in keeping with previous reports[6,7]), TNF was detected in only 17 patients on the first day of admission and in eight by the second day. This finding may be accounted for by the short half-life of serum TNF and the fact that blood for TNF estimation was sampled only once per day. Other authors have suggested that TNF appears transiently and repetitively in the circulation and thus the peak concentration of TNF could easily be missed by infrequent blood sampling[24]. In contrast, soluble TNF receptors were detected in all patients, with a progressive increase in the median concentration of both $sTNFR_{55}$ and $sTNFR_{75}$ being observed among patients who had mild disease, those who developed a local pancreatic complication alone and those who developed organ failure (*Figs 1* and *2*). Spinas and co-workers[11] demonstrated a significant correlation between peak serum TNF and $sTNFR_{55}$ in human volunteers after intravenous administration of *Escherichia coli* endotoxin, suggesting that $sTNFR_{55}$ may reflect the degree of TNF-induced inflammation. If this assumption is correct, the finding in the present study of increased soluble TNF receptors on admission in patients who subsequently develop severe acute pancreatitis would support the contention that TNF is an important central mediator of a systemic inflammatory response with progression to multiple organ failure early in the course of the disease.

IL-6 has also been implicated in the pathogenesis of multiple organ failure[25]. In the present study IL-6 was detectable more often than TNF, being present in the serum of 34 patients on day 1 and in 35 on day 2, with a progressive increase in the median concentration of IL-6 in patients with mild disease, a local pancreatic complication alone or organ failure (*Fig. 3*). Furthermore, IL-6 was detectable by day 2 of admission in the ten patients who developed organ failure. Patel and co-workers[26] found that serum IL-6 levels in patients with the sepsis syndrome from an intra-abdominal septic focus were greater on enrolment in those who subsequently died compared with levels in survivors. Furthermore, the non-survivors had a greater incidence of organ failure relative to that of survivors. The authors have recently demonstrated prolonged upregulation of IL-6 release from peripheral blood mononuclear cells isolated from patients with acute pancreatitis who develop severe disease compared with that in patients with mild disease (A. C. de Beaux *et al.*, unpublished results), which demonstrates the possible contribution of leucocyte activation to the increase in serum IL-6 concentration. The importance of leucocytes mediating organ damage was demonstrated by Barie and co-workers[27] in a sheep model of acute pancreatitis. Leucocyte depletion before induction of pancreatitis prevented pulmonary microvascular changes typical of acute lung injury.

In the present study, serum concentrations of CRP were unhelpful on the first day of admission in predicting disease outcome (*Table 1*). By the second day, however, the median serum concentration of CRP was significantly increased in patients who subsequently developed organ failure compared with that in those with mild disease or a local pancreatic complication alone. This finding concurs with those of other authors who report a rise in the serum concentration of CRP in patients with acute pancreatitis who develop severe disease[15–17]. This is consistent with the concept of a systemic inflammatory response contributing to the development of organ failure in critical illness[19].

Patients dying from acute pancreatitis appear to do so as a consequence of multiple organ failure[1,28]. While such organ failure is usually associated with pancreatic inflammation and necrosis, development of a local pancreatic complication alone in the absence of organ failure is rarely fatal[1]. The present study shows that severe acute pancreatitis is associated with increased levels of serum markers of a systemic inflammatory response and that, within this group of patients, those who develop organ failure show a greater concentration of these markers than those who develop local pancreatic complications alone. The serum markers of inflammation that were measured may have derived from tissues, endothelial cells or leucocytes but the source of these mediators cannot be identified in the study described here. Nevertheless, the findings reflect the host systemic response to pancreatic inflammation and the level of the response did relate to the development of organ failure. While there is evidence to suggest that the host response to pancreatic inflammation may have a significant genetic predetermination[29], further study of the mechanisms leading to a systemic inflammatory response may allow early identification of patients at risk and thereby aid the development of therapeutic intervention to modify the biological response in patients with acute pancreatitis.

Acknowledgements

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Surgical workshop

Reconstruction of a new inferior vena cava after right atrial disruption during recipient hepatectomy

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Polycystic liver disease is a rare indication for liver transplantation[1,2]. Recipient hepatectomy appears to be the most challenging part of the surgical procedure[3]. This is especially true in patients suffering from polycystic liver disease, who may have extremely large livers (up to 15 kg). In these patients hepatectomy and, particularly, dissection of the suprahepatic inferior vena cava (IVC) may be difficult. Management of a disrupted suprahepatic IVC, including a tear of the right atrium, during hepatectomy for polycystic liver disease is described.

Surgical technique

A 54-year-old woman suffered from polycystic kidney and liver disease. She was considered for combined liver and kidney transplantation because of increasing fatigue, cachexia and shortness of breath. Her renal function deteriorated progressively and chronic haemodialysis was started in July 1994. The combined transplantation was performed on 6 November 1994. The donor liver displayed normal anatomy. At recipient operation the huge polycystic liver reached from the right lateral to the left lateral abdominal wall and from the diaphragm to the os pubis. Recipient hepatectomy began with dissection of the hepatoduodenal ligament. A portal vein cannula for venovenous bypass was inserted and the bypass was started as early as possible using left femoral and axillary vein. Then the infrahepatic IVC was encircled and directly transected. With the haemodynamic stability afforded by the venovenous bypass, the retrohepatic IVC was dissected. During final mobilization of the liver from the hepatic fossa the whole liver was attached only by the suprahepatic IVC at the diaphragm. The recipient's liver weight was 14600 g.

After hepatectomy and inspection of the vena cava, it became obvious that no intact endothelium of the IVC was visible; the vascular integrity was maintained only by adventitial tissue. However, the IVC was controlled by the vascular clamp without bleeding. To achieve intact endothelium, which could be used for anastomosis, the IVC was dissected intrapericardially. Surprisingly, this part of the IVC as well as the neighbouring right atrium had no intact endothelium. Consequently the right atrium was clamped further cranially and obliquely in several steps until intact endothelium could be seen. Fortunately the coronary sinus was not affected; haemodynamics were stable. As the endothelial defect was so extensive, direct anastomosis between the donor IVC and the atrium was not feasible.

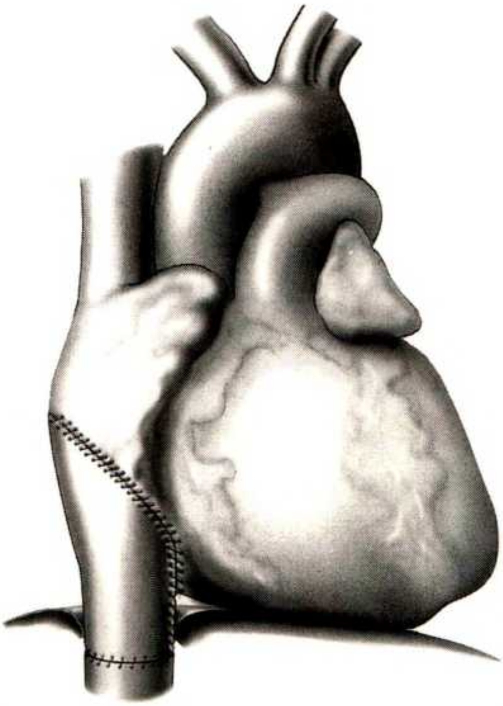

Fig. 1 A large autologous pericardial patch was used for reconstruction of a new inferior vena cava (IVC). The donor suprahepatic IVC was anastomosed directly to this reconstruction

The atrium and part of the IVC were reconstructed with a large autologous pericardial patch, shaped and sutured as a tube (*Fig. 1*). The donor suprahepatic IVC was then anastomosed directly to this reconstruction. Liver transplantation was continued as usual. The donor kidney was transplanted following liver transplantation.

After operation both grafts showed good function from the beginning. Heparin was given immediately after operation to keep the activated partial thromboplastin time between 60 and 80 s. The patient was extubated on the second postoperative day. Right heart catheterization performed on day 8 after surgery revealed no pressure gradient across the atrial reconstruction. The postoperative course was prolonged due to general cachexia. Finally, 106 days after operation, the patient was discharged in good condition with normal liver and kidney function.

Discussion

This case shows that hepatectomy in patients with polycystic liver disease can lead to serious problems and should therefore be performed with great care. No general recommendation for the best technical approach is possible, and this has to be decided for each case. Special attention should be directed towards the suprahepatic IVC. The abnormal liver weight can cause dangerous tension to this vessel, and to the heart during mobilization. The suprahepatic IVC should be transected before the enlarged liver is moved out of the liver bed. When this becomes troublesome, early sternotomy and dissection of the IVC intrapericardially can be advantageous. Autologous pericardium has been helpful in

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various cardiovascular procedures[4] and was suitable for atrial reconstruction in the case presented here.

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Randomized study of antibiotic prophylaxis for general and gynaecological surgery from a single centre in rural Africa

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In a district rural hospital in Uganda, 850 surgical patients were evaluated prospectively over a 3-year period to compare the clinical efficacy of conventional postoperative penicillin therapy with single-dose ampicillin prophylaxis for hernia repair and ectopic pregnancy, and with single-dose ampicillin–metronidazole prophylaxis for hysterectomy and caesarean section. The high rate of postoperative infection usually encountered in African hospitals after conventional treatment with penicillin for 7 days was significantly reduced with the new regimen: from 7·5 to 0 per cent in hernia repair and from 10·7 to 2·4 per cent in ectopic pregnancy; from 20·0 to 3·4 per cent in hysterectomy and from 38·2 to 15·2 per cent in caesarean section. Length of hospital stay and postoperative mortality rates were also significantly reduced. Single-dose ampicillin prophylaxis with or without metronidazole, although rarely used in developing countries, is more cost effective than standard penicillin treatment.

The role of surgery in developing countries is well recognized, and progress has been made in identifying surgical needs, suitable operative techniques and facilities[1,2].

A major concern is postoperative wound and deep infection. Poor sterility and hygiene of operating theatres and wards, lack of trained personnel and delayed patient attendance to the hospital are among factors contributing to the high rate of postoperative infection in developing countries. In subSaharan Africa a record of postoperative infection is rare and few studies are available[3], but a rate of 40–70 per cent is not exceptional[4–7].

This study, performed at Hoima District Hospital (western Uganda), investigated the prophylatic use of ampicillin for elective and emergency hernia repair and ectopic pregnancy, and ampicillin–metronidazole for elective and emergency hysterectomy and caesarean section, and compared this regimen with postoperative penicillin treatment.

A large number of trials have shown that antimicrobial prophylaxis is effective in reducing the incidence of postoperative wound infection but all the studies have been carried out in industrialized environments. Most studies include only elective surgery on properly assessed and selected patients, with timely diagnosis and proper preparation for surgery[8–16]. This study is one of the few performed in a developing country, in a high-risk environment, including many emergency surgical procedures often performed on patients who presented late in the course of the illness.

Patients and methods

Over the 3-year period from 1991 to 1993, 850 consecutive adult patients (aged over 18 years) admitted to Hoima Hospital for both elective and emergency surgical procedures were eligible for the study.

Hoima Hospital is a 150-bed government institution supported by International Service Volunteers' Association (Italian Cooperation), where more than 800 major surgical procedures are performed yearly, mainly in general and obstetric surgery, 35 per cent as an emergency. Six Ugandan and two Italian surgeons perform the surgery. No microbiological facilities are available locally and therefore no cultures were obtained from infected wounds

After obtaining written consent, patients were divided into two categories according to the surgical condition. The first group included 479 patients: 229 had inguinal hernia repair without intestinal resection or tissue necrosis (161 elective, 68 emergency) and 250 had surgery for ectopic pregnancy (all emergencies) The second group consisted of 371 patients: 177 had total abdominal hysterectomy (95 for cervical cancer, 82 for fibroids; all elective) and 194 had caesarean section (116 emergency, 78 elective).

Patients were allocated by means of random numbers to antibiotic prophylaxis as follows: half the patients with hernia or ectopic pregnancy received a single dose of ampicillin 2 g intravenously at induction of anaesthesia (30 min before surgery), while the remainder received the standard postoperative treatment of intramuscular fortified procaine penicillin 1 2 megaunits daily for 7 days (starting about 3 h after surgery).

Of patients undergoing hysterectomy or caesarean section, 192 were randomized to receive a single dose of ampicillin 3 g intravenously plus metronidazole 500 mg at induction of anaesthesia, while the remainder (179) received benzylpenicillin 1 megaunit intravenously every 6 h for 1 day (starting about 3 h after surgery), followed by fortified procaine penicillin 1·2 megaunits daily for 6 days.

A group receiving placebo was not included since previous experience showed an unacceptably high rate of postoperative infection

Imperfect balance between the groups resulted from the elimination of a few patients for whom treatment procedures were not strictly observed (additional self-medication, irregular treatment and self-discharged patients)· 12 patients operated on for hernia repair and eight for caesarean section, all receiving penicillin therapy

There were no differences between patient groups with respect to general and nutritional status, preoperative preparation, administration of anaesthesia (spinal for hernia repair and caesarean section, thiopentone–suxamethonium–ether with endotracheal tube for ectopic pregnancy and hysterectomy), skin disinfection (iodine), intravenous fluid therapy (for 24 h only) and management of dressings (daily with chlorhexidine). Likewise, other minor prognostic variables were similar between the groups, including the presence of a urethral catheter for 24 h (only the hernia group was without), anaemia (haemoglobin concentration less than 10 g/dl), blood transfusion and reasons for caesarean section

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After operation each patient was carefully assessed each day by two supervisors aware of the type of prophylaxis used.

Further follow-up was performed 2 weeks after hospital discharge to detect delayed infections; compliance greater than 90 per cent was achieved in all groups, although cash incentives were necessary.

Criteria for infection were pyrexia above 38°C twice within 24 h (excluding the first 24 h), urinary tract infection diagnosed if symptoms were present, together with a positive leucocyte count (more than 15 per field on urine microscopy), urine culture was not available.

Wound infections were graded according to the classification of Karl *et al.*[17]: grade 1, superficial infection (cellulitis with minimal purulent exudate); grade 2, deep infection (cellulitis with moderate purulent infection), grade 3, infection throughout the wound with or without dehiscence.

Peritonitis was deemed to be present when clinical signs and symptoms (fever, abdominal tenderness and pain with increased leucocytosis) were evident. The length of stay and postoperative outcome were recorded. Cost factors were analysed, including both the simple cost of the two different regimens and additional costs related to any increased length of hospital stay.

Results are expressed as mean(s.d.). For statistical comparison, the χ^2 test with Yates' correction and Fisher's exact test were used. For calculation of differences in postoperative stay, analysis of variance was performed. $P<0{\cdot}05$ was considered significant.

Results

In patients who received ampicillin, postoperative morbidity was significantly reduced compared with those receiving penicillin. The overall rate of infective complications was reduced from 7·5 to 0 per cent after hernia repair ($P=0{\cdot}001$), from 10·7 to 2·4 per cent after surgery for ectopic pregnancy ($P=0{\cdot}013$), from 20·0 to 3·4 per cent after hysterectomy ($P=0{\cdot}001$) and from 38·2 to 15·2 per cent after caesarean section ($P<0{\cdot}001$). There were three postoperative deaths, all in patients following caesarean section who received penicillin prophylaxis (P not significant) (*Tables 1* and *2*). There were no serious infective complications after surgery for hernia or ectopic pregnancy when ampicillin was used compared with deep infection, dehiscence and peritonitis in 10 patients when penicillin was employed. The incidence of fever was also reduced.

The mean postoperative hospital stay was significantly shortened by the use of preoperative ampicillin both in patients having hernia repair (from 7·9 to 6·2 days, $P<0{\cdot}001$) and in those with ectopic pregnancy (from 8·9 to 7·0 days, $P<0{\cdot}001$).

Similarly, in patients who had hysterectomy or caesarean section, postoperative infective complications were less severe and significantly fewer episodes of peritonitis and wound dehiscence were recorded in those who received ampicillin with metronidazole at the time of caesarean section.

The cause of the three postoperative deaths after caesarean section was purulent peritonitis complicated by septic shock (the patients presented late after prolonged labour with ruptured membranes in the village; moreover one was markedly anaemic). One patient required a secondary laparotomy and two were managed conservatively.

The duration of postoperative stay was shorter for

Table 1 Clinical features of patients with hernia and ectopic pregnancy treated with prophylactic ampicillin or postoperative penicillin

	Ampicillin	Penicillin	P
Superficial wound infection*			
Hernia	0 (0)	4 (3·7)	0·04†
Ectopic pregnancy	3 (2·3)	6 (4·9)	n.s.‡
Deep wound infection*			
Hernia	0 (0)	4 (3·7)	0·05†
Ectopic pregnancy	0 (0)	5 (4·1)	0·03†
Peritonitis*			
Hernia	0 (0)	0 (0)	
Ectopic pregnancy	0 (0)	1 (0·8)	n.s.‡
Urinary tract infection*			
Hernia	0 (0)	0 (0)	
Ectopic pregnancy	0 (0)	1 (0·8)	n.s.‡
Wound dehiscence*			
Hernia	0 (0)	2 (1·8)	n.s.‡
Ectopic pregnancy	0 (0)	0 (0)	
Fever*			
Hernia	3 (2·4)	18 (17·0)	<0·001‡
Ectopic pregnancy	15 (11·6)	21 (17·3)	n.s.‡
Postoperative death*			
Hernia	0 (0)	0 (0)	
Ectopic pregnancy	0 (0)	0 (0)	
Mean(s.d.) postoperative stay (days)			
Hernia	6·2(1·2)	7·9(2·1)	<0·001§
Ectopic pregnancy	7·0(1·0)	8·9(1·1)	<0·001§

In all, 123 patients undergoing hernia repair received ampicillin and 106 had penicillin; 129 having surgery for ectopic pregnancy received ampicillin and 121 penicillin *Values in parentheses are percentages. †Fisher's exact test; ‡χ^2 test with Yates' correction; §analysis of variance; n.s., not significant

Table 2 Clinical features of patients undergoing hysterectomy and caesarean section

	Ampicillin plus metronidazole	Penicillin	P
Superficial wound infection*			
Hysterectomy	2 (2)	6 (7)	n.s.‡
Caesarean section	9 (8·5)	10 (11)	n.s.‡
Deep wound infection*			
Hysterectomy	1 (1)	8 (9)	0·03†
Caesarean section	6 (6·7)	17 (19)	0·008‡
Peritonitis*			
Hysterectomy	0 (0)	4 (4)	n.s.‡
Caesarean section	0 (0)	5 (6)	0·02†
Urinary tract infection*			
Hysterectomy	0 (0)	0 (0)	
Caesarean section	1 (1)	2 (2)	n.s.‡
Wound dehiscence*			
Hysterectomy	0 (0)	4 (4)	n.s.‡
Caesarean section	0 (0)	6 (7)	0·008†
Fever*			
Hysterectomy	9 (10)	30 (33)	<0·001‡
Caesarean section	27 (25·7)	47 (53)	<0·001‡
Postoperative death*			
Hysterectomy	0 (0)	0 (0)	
Caesarean section	0 (0)	3 (3)	n.s.‡
Mean(s.d.) postoperative stay (days)			
Hysterectomy	7·7(1·5)	9·0(1·4)	0·007§
Caesarean section	7·8(1·6)	12·4(2·5)	<0·001§

In all, 87 patients undergoing hysterectomy received ampicillin plus metronidazole and 90 received penicillin, 105 having caesarean section received ampicillin–metronidazole and 89 penicillin *Values in parentheses are percentages †Fisher's exact test, ‡χ^2 test with Yates' correction; §analysis of variance; n.s., not significant

Table 3 Cost analysis of regimens

Regimen	Treatment cost (US$)	Admission day cost (US$)	Mean duration of hospital stay (days)		Total cost per single patient (treatment plus admission) (US$)	
Ampicillin (2 g)	0·5	3·0	7·0 (ectopic pregnancy)	6·2 (hernia)	21·5 (ectopic pregnancy)	19·1 (hernia)
Procaine penicillin (1·2 megaunits for 7 days)	0·7	3·0	8·9 (ectopic pregnancy)	7·9 (hernia)	27·4 (ectopic pregnancy)	24 4 (hernia)
Ampicillin (3 g) plus metronidazole (500 mg)	1·7	3·0	7 8 (caesarean section)	7·7 (hysterectomy)	25·1 (caesarean section)	24·8 (hysterectomy)
Benzylpenicillin (4 megaunits) plus procaine penicillin (1 2 megaunits for 6 days)	2·1	3·0	12·4 (caersarean section)	9·0 (hysterectomy)	39·3 (caesarean section)	29·1 (hysterectomy)

Costs taken from *The International Dispensary Association Price Indicator* May 1993 (PO Box 3098, 1003 AB Amsterdam, The Netherlands)

patients in the ampicillin–metronidazole group than for those in the penicillin group: 7·7 *versus* 9·0 days after hysterectomy ($P = 0{\cdot}007$) and 7·8 *versus* 12·4 days after caesarean section ($P < 0{\cdot}001$).

In 1992 in Hoima Hospital the running cost for a single admission day was US$3·0 (*Table 3*); this was inclusive of allocated costs of personnel, drug, supplies and utilities divided by the number of admission days for the period. Since the duration of postoperative stay was shorter for both groups of patients receiving ampicillin prophylaxis, there was a cost saving. In addition, the ampicillin–metronidazole regimens were cheaper than the full penicillin course. Not only was there a cost advantage, but the indirect cost of suffering related to infective complications and absence of the patient and attendants from the domestic environment were minimized.

Discussion

Postoperative infection rates in developing countries can reach astonishing levels. They are often underestimated and little documentation is available[3–5]. This high rate is not unavoidable, even in a poorly equipped environment, and all the factors leading to infection can systematically be influenced.

This study in rural Uganda confirms what has been already proved in Western countries: that appropriate antibiotic prophylaxis is effective in reducing the postoperative morbidity rate in clean general surgery and gynaecology operations[18,19].

This short-course, single-dose antibiotic prophylaxis may not be optimal if significant contamination is present during the operation: care was taken to exclude from the protocol patients with established sepsis at the time of surgery.

Penicillin treatment, in spite of the narrow spectrum of antibacterial activity, is the most widely used method of prophylaxis in Ugandan and African district hospitals[5,19]. The reasons are that penicillin-resistant bacteria are less common than elsewhere, more appropriate antibiotics are not easily available, facilities for microbiological tests are rare and postoperative follow-up is difficult. In this study ampicillin was chosen for its low cost, broad spectrum, sufficient half-life and high wound concentration. Metronidazole was selected for its anaerobic activity and long half-life[5,20–22]. Resistance to either antibiotic is still rare in rural Africa.

Postoperative infection was reduced to acceptable rates by the use of prophylaxis. The high rate after caesarean section reflects the poor socioeconomic status of the obstetric patients, characterized by undetected antenatal risk factors and delayed surgery until obstructed labour was obvious[5].

The cost of the new regimen was lower than that of postoperative penicillin and thus reduced overall expense[14,23]. This cost advantage and the reduced length of hospital stay provide further proof that prophylactic use of appropriate antibiotics significantly reduces the morbidity rate in rural hospitals in developing countries after general and gynaecological surgery.

Acknowledgements

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Effect of transcutaneous electrical muscle stimulation on postoperative muscle mass and protein synthesis

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In an experimental study, 13 patients undergoing major elective abdominal surgery were given postoperative transcutaneous electrical muscle stimulation (TEMS) to the quadriceps femoris muscle on one leg; the opposite leg served as control. Changes in cross-sectional area (CSA) and muscle protein synthesis were assessed by computed tomography and ribosome analysis of percutaneous muscle biopsies before surgery and on the sixth postoperative day. The percentage of polyribosomes in the ribosome suspension decreased significantly ($P < 0{\cdot}03$) after operation in control legs, but not in stimulated legs ($P > 0{\cdot}16$). The total concentration of ribosomes decreased significantly in legs treated with TEMS ($P < 0{\cdot}03$) but not in control legs ($P > 0{\cdot}16$). CSA decreased significantly in both legs. The decrease in polyribosomes and CSA after operation was significantly less in stimulated legs than in controls ($P < 0{\cdot}05$). TEMS may be a simple and effective method for improving muscle protein synthesis and muscle mass after abdominal surgery and should be evaluated in other catabolic states with muscle wasting.

After surgical trauma, starvation and immobilization, muscle protein is wasted because of dysregulation in protein metabolism with reduced muscle protein synthesis and unchanged or enhanced degradation[1–6]. Since loss of muscle protein will reduce muscle function and because postoperative convalescence and fatigue may be related to loss of muscle mass and function[7], preservation of skeletal muscle protein is of major clinical importance. Previous attempts to prevent the decrease in the postoperative loss of muscle tissue and function have been based primarily on nutritional support. Although nutrition[8–10] or treatment with anabolic hormones such as insulin[11] and growth hormone[12–13] can reduce protein catabolism and loss of muscle mass, these methods have not been demonstrated to have clinically important effects on postoperative muscle function and convalescence. It is well established that muscle activity is important for muscle tissue anabolism[14] and that immobilization leads to loss of muscle mass and function[15]. Unfortunately, immobilization is a part of surgical convalescence and therefore contributes to loss of muscle mass and delayed recovery.

Transcutaneous electrical muscle stimulation (TEMS) is an established method for providing muscle activity[16] and has been demonstrated to increase muscle protein synthesis and growth in immobilized patients[17–18]. The purpose of the present study was therefore to investigate the effect of TEMS on muscle protein synthesis and mass of the quadriceps femoris muscle after major abdominal surgery.

Patients and methods

Thirteen patients (seven women, six men; median age 55, (range 27–73) years) scheduled for elective abdominal surgery were studied. Informed written consent to participate was obtained from all patients and the study protocol was approved by the Copenhagen ethics committee. Operative procedures were ten colonic resections, one abdominoperineal resection, one vagotomy and pyloroplasty and one gastric resection. All patients received general anaesthesia and had postoperative epidural analgesia with low-dose bupivacaine and morphine[19] for 96 h. Patients were allowed liquid oral intake immediately after operation and all had normal food intake within 4 days after surgery. Ambulation was started on the first postoperative day aiming at 3 h on day 1, 6 h on day 2 and more than 8 h on day 3. No patient had postoperative complications.

Electrical stimulation

TEMS was started in the morning on the day after surgery. It was given to the quadriceps femoris on one leg, the right in 12 patients on the left in one patient; the other leg served as a control. Stimulation was given for 1 h three times a day for 5 days using a portable battery-powered stimulator (Elpha 2000; Danmeter, Odense, Denmark) using two self-adhesive electropads of size 50 × 90 mm. One electrode was placed over the proximal part of the thigh 10 cm below the inguinal ligament and the other 8 cm above the patella. The electrodes remained in the same position for all 5 days of stimulation, which was provided with a pulse rate of 30 Hz, pulse width 250 μs, rise time 2 s, on-time 5 s and a pause of 10 s. The amplitude was adjusted to produce a visible muscle contraction, and was controlled twice daily by the investigators.

Computed tomography

Patients were examined on the day before surgery and on the sixth postoperative day with computed tomography (CT) of both legs for assessment of the cross-sectional area (CSA) of the quadriceps femoris muscle 20 cm above the patella. Patients were examined in the supine position and the CT gantry was set to obtain one 8-mm thick slice perpendicular to the axis of the femur. For each scan CSA was measured five times for each leg and the mean value was calculated. Fat and bone tissue were excluded from measurements by using Hounsfield units between zero and 100. The CT and CSA calculation were performed by one examiner, who was blinded to the side of electrical stimulation. The coefficient of variation by objective CT assessment is in the range of 3 per cent[20].

Muscle biopsy

Percutaneous muscle biopsies were taken with a Bergstrom needle on both sides from the lateral portion of the quadriceps

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femoris muscle immediately after induction of anaesthesia but before surgery, and under local anaesthesia on the sixth postoperative day.

Ribosome analysis

The muscle specimens were stored at −80°C and transported from Copenhagen to Stockholm on dry ice. Total storage time was less than 5 weeks in all cases. All four muscle specimens from the same patient were analysed simultaneously. The techniques used for the isolation of ribosomes and for determination of their size distribution have been described in detail previously[21]. The frozen muscle biopsy of approximately 80 mg wet-weight was homogenized in a standardized manner in a medium containing an RNAse inhibitor. After centrifugation the supernatant, containing the ribosomes, was ultracentrifuged in an angle rotor to separate the ribosomes from particles of lower molecular weight. The resulting ribosome pellet was resuspended and the total ribosome concentration was measured by absorbance at 260 nm. The concentration was expressed as optical density (OD) units per milligram tissue. A portion of the ribosome suspension was then placed onto a linear density gradient of sucrose. After ultracentrifugation in a swing-out rotor, the gradient was pumped through a continuous flow cuvette and the absorbance was monitored at 260 nm. The total area under the absorbance curve was determined. The peaks representing the ribosomal subunits and monoribosomes were identified as well as the area corresponding to the polyribosomes. The percentage of polyribosomes from total ribosomes was calculated. The coefficient of variation for the total ribosome concentration as well as for the percentage of polyribosomes was below 6 per cent[22].

Statistical analysis

The Wilcoxon signed rank test for paired data was used to determine statistical significance between legs and between preoperative and postoperative changes on each leg. $P<0{\cdot}05$ was considered significant. Data are given as mean(s.e.m.).

Results

All 13 patients completed the TEMS programme with CT before and 6 days after surgery but only ten patients had a complete set of muscle biopsies. In three patients muscle biopsies were technically insufficient (defrosted in two patients and contained large amounts of fat in one).

Total ribosome concentration

Before operation, the mean(s.e.m.) total concentration of ribosomes was similar in the two legs (35·5(2·8) *versus* 33·1(1·5) OD units per mg wet-weight for stimulated legs *versus* controls; ($P>0{\cdot}5$). On the sixth postoperative day there was an insignificant decrease in total ribosome concentration in the control legs compared with preoperative values (33·1(1·5) *versus* 28·3(2·4) OD units/mg; $P>0{\cdot}16$), while the difference in legs treated with TEMS was significant (35·5(2·8) *versus* 28·7(1·6) OD units/mg; $P<0{\cdot}03$). There was no difference in postoperative decrease in total ribosome concentration between stimulated and control legs (6·8(3·1) *versus* 4·8(2·4) OD units/mg; $P>0{\cdot}6$).

Polyribosomes

The percentage of polyribosomes was similar in both groups of legs before operation (mean(s.e.m.) 50·6(0·8) *versus* 50·2(1·0) per cent for stimulated and control legs respectively, $P>0{\cdot}6$) (*Fig. 1*). On the sixth postoperative day there was a significant decrease in polyribosomes in the control legs compared with preoperative values (50·2(1·0) *versus* 46·3(1·5) per cent; $P<0{\cdot}03$). In contrast, there was a small and insignificant postoperative decrease in the legs treated with TEMS (50·6(0·8) *versus* 48·2(1·5) per cent; $P>0{\cdot}16$). The postoperative decrease in

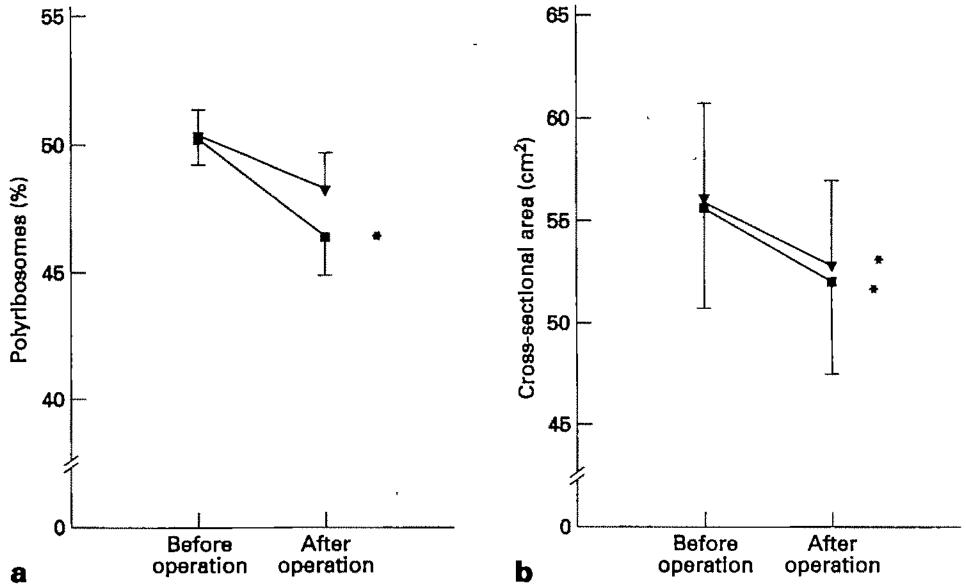

Fig. 1 **a** Polyribosomes as a percentage of total ribosomes in muscle biopsies ($n=10$) and **b** cross-sectional area of the quadriceps femoris muscle ($n=13$) in legs treated with TEMS (▼) and control legs (■). Values are mean(s.e.m.). *$P<0{\cdot}05$ *versus* preoperative values (Wilcoxon signed rank test) polyribosomes was significantly larger in control legs than stimulated legs (3·9(1·5) *versus* 2·4(1·4) per cent; $P < 0{\cdot}05$).

Computed tomography

The mean(s.e.m.) preoperative CSAs of the quadriceps femoris muscle were similar in treated and control legs (56·0(4·9) *versus* 55·6(5·0) cm^2 respectively; $P > 0{\cdot}7$). Six days after operation there was a significant decrease in CSA in stimulated legs to 52·7(4·3) cm^2 ($P < 0{\cdot}0012$) and in control legs to 51·9(5·0) cm^2 ($P < 0{\cdot}0002$). The postoperative decrease in CSA was significantly greater in control legs than stimulated legs ($P < 0{\cdot}04$).

Discussion

These results show that 5 days of TEMS may have reduced postoperative loss of muscle mass and decreased muscle protein synthesis as expressed by the smaller decrease in polyribosome concentration and smaller reduction in CSA of the quadriceps femoris muscle, while the decrease in total ribosome concentration in muscle was not affected.

The postoperative loss of muscle is a combined effect of the catabolic response to surgical injury, immobilization and reduced nutritional intake, all of which have similar effects on muscle metabolism[1–6]. Therapeutic effects have therefore aimed at reducing the surgical stress response by neural blockade techniques and pain relief[7] and nutrition[8–10], all of which have been documented to have positive effects on protein synthesis and catabolism, although they have not been able to prevent the catabolic changes.

Muscle protein metabolism *in vivo* in humans may be examined by a variety of techniques. In this study muscle protein mass was reflected by the CSA and protein synthesis by ribosome measurement. Because synthesis and degradation of muscle proteins are regulated independently it is preferable to study these processes by independent techniques. The ribosome technique is qualitative in character and gives a good quantitative estimate of how the machinery for protein synthesis changes. Protein synthesis rate can only be estimated in quantitative terms, by isotope incorporation techniques. Unfortunately, there is controversy concerning the definitions and sampling of the immediate precursor pool of amino acids used for protein synthesis[23]. Protein degradation is also difficult to estimate. The efflux of 3-methylhistidine from the leg gives information regarding the degradation of contractile proteins, but plasma flow measurements may be problematic especially when measurements are performed 6 days apart. In future, determination of protease activity combined with measurement of the transcription of key enzymes may be a useful tool for studying protein degradation.

TEMS obviously interferes with protein synthesis. However, the difference between treated and control legs was only marginal with respect to the total ribosome concentration, reflecting an unmodified total capacity for protein synthesis. The protein synthetic activity, on the other hand, as indicated by the activity of the existing ribosome population, was significantly better preserved in the leg given TEMS (*Fig. 1*). These results suggest a positive effect on protein synthesis, but whether degradation is influenced cannot be deduced from the present data. Since TEMS only had a slightly positive effect on muscle mass and protein metabolism, future studies should consider more prolonged stimulation.

Spontaneous muscle activity (exercise and mobilization) may be reduced after major operations, so TEMS may be a suitable method for reducing postoperative loss of muscle tissue. This is supported by studies showing muscle contractile activity (exercise) to produce an increase in muscle protein synthesis during restricted energy intake[24], disuse muscle atrophy[17] and *in vitro* glucocorticoid-induced skeletal muscle atrophy[25]. Furthermore, TEMS has been used in rehabilitation and as an adjunct to strength training[16]. It is well known that repeated muscular contractile activity, both as voluntary contractions or provided with electrical stimulation, leads to increased muscle protein synthesis and hypertrophy[18,26,27]. TEMS treatment is simple, inexpensive and without discomfort during stimulation. None of the present patients complained of the treatment, which could be performed during short-term sleeping periods in the afternoon. Since TEMS can be used in immobilized patients, such as in intensive care patients, the apparent anabolic effect should be studied in other patient groups with catabolic illness and muscle wasting. Ultimately, the clinical value of TEMS will depend on whether this technique can achieve preservation or enhancement of muscle function and reduction of surgical convalescence and fatigue.

In conclusion, TEMS may be a simple and effective method of reducing muscle waste and catabolism after abdominal surgery.

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Short note

Randomized comparison of agents for caudal anaesthesia in anal surgery

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First described by Sicard and Cathelin in 1901, caudal anaesthesia is readily applicable to minor anorectal surgery[1].

Patients and methods

Some 90 patients with anorectal lesions were recruited to the study, 54 men (mean age 48 years) and 36 women (mean age 35 years). Two were excluded: one did not consent and one had abnormal sacral anatomy. The remaining 88 patients had a total of 92 minor anal procedures including haemorrhoidectomy and fissure or fistula surgery. The patients were randomized into three groups. Group 1 received 1 per cent lignocaine with 1:100000 adrenaline (30 procedures), group 2, 2 per cent lignocaine (31 procedures) and group 3, 2 per cent lignocaine with 1:100000 adrenaline (31 procedures).

Caudal anaesthesia was established by trained surgeons using a standard 20-G hypodermic needle with the patient in a prone position. The onset, duration and complications of anaesthesia were monitored. Statistical analysis was performed with two-way *t* test and included determination of confidence intervals.

Results

The caudal injection was successful in producing anaesthesia at the first attempt in 90 per cent of patients and after a second attempt in 9 per cent. Anaesthesia was abandoned in one patient who had a dural puncture, when mild leg weakness was noted. This settled early in the postoperative period. There was epidural vascular penetration in seven patients (8 per cent) as shown by aspiration of blood. The needle was repositioned and after further test aspiration, the caudal injection was given. Intravenous injection occurred in one patient who developed immediate tonic convulsions which were treated with intravenous diazepam. Recovery was uneventful thereafter. No patient required supplementary anaesthesia.

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Anaesthetic latency was shortest (5 ± 2·5 min) and the duration longest (91 ± 2 min) in patients who received 2 per cent lignocaine with adrenaline (*Fig. 1*). On direct questioning, seven of eight patients who previously had similar surgery under general anaesthesia preferred the caudal technique. Three others who had not had similar anal surgery previously were dissatisfied with caudal anaesthesia on account of either a preference for being unconscious or dissatisfaction with the position used for surgery.

Discussion

Caudal anaesthesia is simple and economical. The success rate in this study was 99 per cent, higher than usually quoted for this technique[2]. This might be related to racial differences in sacral anatomy which render caudal anaesthesia easier in negroes, the racial group of all these patients[3]. The incidence of vascular penetration is lower when short-bevelled (caudal) needles are used[2]; the high incidence in this study may have been due to the hypodermic needles. Dural puncture may result from the use of long needles or an abnormal dural extension[1].

Although the differences in the onset and duration of anaesthesia were statistically significant, 1 per cent lignocaine with adrenaline still gave adequate anaesthesia for

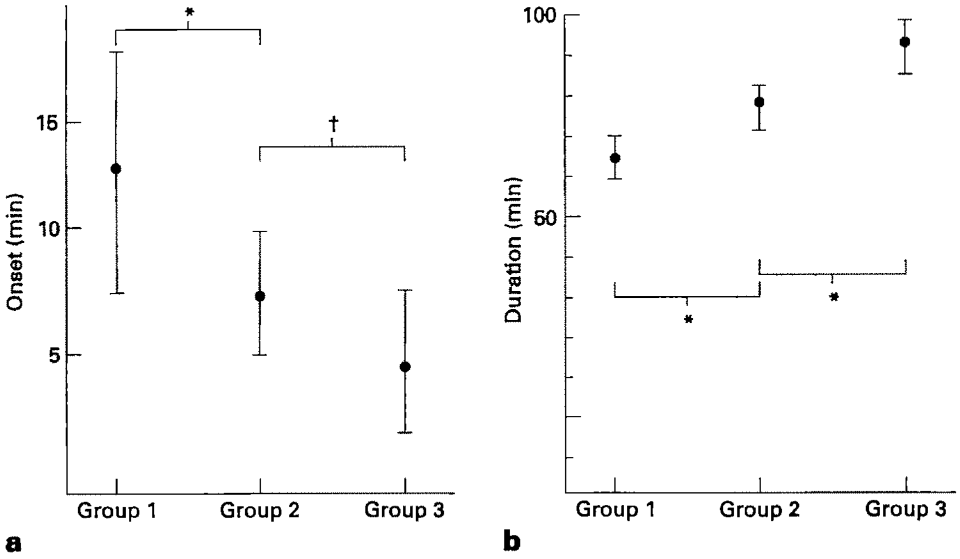

Fig. 1 a Onset and b duration of caudal anaesthesia in patients given 1 per cent lignocaine with 1:100000 adrenaline (group 1), 2 per cent lignocaine (group 2) or 2 per cent lignocaine with 1.100000 adrenaline (group 3). *$P<0·001$; †$P>0·01$

all the procedures, with little risk of toxicity, a concern often expressed about 0·5 per cent bupivacaine, an alternative drug used in this setting. No drug-related complications occurred. Patient acceptability was high (96 per cent), and any who, in future, prefer to be unconscious could have sedation.

The low cost, minimal requirements, satisfactory anaesthesia and acceptability make caudal anaesthesia a useful option for minor anal surgery.

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Surgical workshop

A better bridge for loop stomas

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Skin irritation is the single most common complication of ileostomy or colostomy and is due to the leakage of effluent on to the parastomal skin[1]. There are a number of bridges available to support loop stomas during initial healing but many are too large for loop ileostomies or small colostomies. They cause difficulties in fitting secure and waterproof appliances while the loop requires support. The first few days of handling a new stoma are crucial in developing the patient's self-confidence, and leakage during this time can have severe psychological consequences[2–4].

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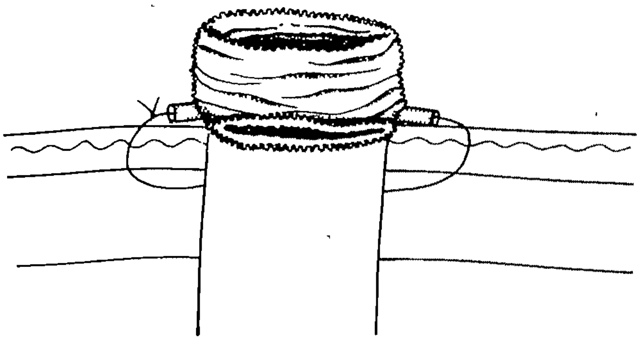

Fig. 1 Loop ileostomy supported by nylon deep tension suture with its sheath as the bridge

A deep tension suture is suggested as a cheap and reliable alternative to a proprietary bridge. The plastic sheath enclosing the suture supports the bowel directly while the nylon suture anchors it to the skin on either side of the stoma (*Fig. 1*). The suture and its sheath are less bulky than any of the proprietary bridges and lie entirely within the cut-away adhesive contact area of the stoma bag. This is always tailored to the bowel and allows easy changing of the appliances while the patient is learning to handle the stoma.

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Perineal excision of the rectum

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An intersphincteric and perimuscular approach was employed for perineal excision of the rectum in 33 patients who had previously undergone total colectomy with preservation of the rectum. Laparotomy was avoided in 28 of the 29 patients who had had closure of the rectal stump with ileostomy. Of the four patients (two with ileorectal anastomoses and two with sigmoid mucous fistulas) for whom laparotomy was planned, this was considered to be much less extensive than would otherwise have been required. It is concluded that in patients who have previously undergone total colectomy for inflammatory bowel disease, subsequent perineal excision of the rectal stump without laparotomy is frequently possible.

When rectal excision becomes necessary in patients who have previously undergone total colectomy and ileostomy with preservation of the rectum, a combined abdominoperineal approach is usually employed. Rectal excision via the perineal route alone has not been described previously for inflammatory bowel disease. This paper reports the experience of a single centre with this method.

Patients and methods

Fourteen men with a median age of 47 (range 23–75) years and 19 women of median age 48 (range 22–70) years were operated on electively The diagnosis was advanced carcinoma of the colon in one patient, Crohn's disease in 27, ulcerative colitis in four and exclusion proctitis in one. The indications were either troublesome secretion from the rectum or shrinkage of the rectum making proctoscopy for exclusion of malignancy impossible. Twenty-nine patients had had an ileostomy, enabling an exclusively perineal approach. The perineal part of the operation had to be accompanied by a laparotomy in four additional patients, two of whom had an ileorectal anastomosis and two a sigmoid mucous fistula. The time between colectomy and rectal excision, operating time, operative blood loss, postoperative complications and duration of hospital stay following rectal excision were recorded. All patients were followed up to obtain information on wound healing and possible impairment of sexual function.

Operative details

The operation commences with a typical intersphincteric excision, as described by Lyttle and Parks[1], up to the level where the mesorectal fat becomes visible Care is taken to stay as close to the rectal wall as possible to avoid pelvic nerve damage. This is made easier by inserting a finger inside the rectum for assessment of the rectal wall thickness, which varies greatly in patients with Crohn's disease. The rectal mesentery is then divided close to the rectal wall as described by Lee and Dowling[2] The elasticity of the tissues usually makes this part of the operation easy but perforation is possible even in cases with perirectal fibrosis due to fistulas or healed abscesses. The peritoneal cavity is entered enabling inspection of the small bowel Any adhesions between the small bowel and the closed rectum are divided. The resection may be simplified by grasping the top of the rectum with a clamp followed by 'downward' dissection. Since the tissues are divided close to the rectal wall, only small vessels are cut and bleeding is easily controlled. Finally, the pelvic floor is closed without drainage and antibiotics (cefotaxime and metronidazole) are given for 5 days after operation.

Results

The median interval from colectomy to excision of the rectum was 3·0 years (range 5 months–8·3 years). Perineal rectal excision was successfully accomplished in 28 of 29 patients. In one male patient technical difficulties necessitated a laparotomy. In patients with ileorectal anastomoses or mucous fistulas, the laparotomy facilitated less extensive intra-abdominal dissection. The median operating time was 110 (range 65–279) min and median operative blood loss was 500 (range 150–1800) ml. An intra-abdominal haematoma occurred in one patient after operation and a postoperative infection in another. Neither required reoperation. At follow-up, the perineal wound had failed to heal in one woman 267 days after operation. One man complained of partial erectile dysfunction (successfully treated with prostaglandin E_1 resulting in normal ejaculation) and one woman experienced temporary dyspareunia. Median hospital stay was 6 (range 3–13) days.

Discussion

In patients with fulminant pancolitis in whom the diagnosis is in doubt and ileorectal anastomosis is inadvisable, panproctocolectomy with ileostomy has been replaced in many centres by colectomy with closure of the rectal stump and ileostomy. In patients with Crohn's colitis, those with recurrent otherwise intractable disease after ileorectal anastomosis, those with troublesome secretion from the rectal stump, and in patients in whom malignancy cannot be excluded rectal excision may be required.

While excision of short rectal stumps is surgical routine, the experience described herein suggests that the abdominal part of the operation can often be omitted. Furthermore, in patients in whom an additional laparotomy is necessary because of technical difficulties, the abdominal phase of the operation is easier because of the diminished requirement for adhesiolysis. Perineal excision of the rectum should be delayed until 3 months after the initial colectomy when the postoperative adhesions have maximally resolved to enable easier and safer dissection with a smaller risk of damaging the small bowel. The incidence of postoperative complications was

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comparable to those of the combined abdominoperineal approach[1–4]. It is therefore concluded that perineal excision of the rectal stump without abdominal dissection is frequently possible in patients with inflammatory bowel disease.

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Salvage surgery for ileal pouch outlet obstruction

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Sixteen patients with ileal pouch outlet mechanical obstruction had major abdominal revision of the ileoanal anastomosis. Before operation all had severe difficulty in evacuation which required catheterization in 11. Eleven patients had a long efferent limb and/or long anorectal cuff, and five had a persistent stricture at the ileoanal anastomosis. None had pouchitis. The pouch was fully mobilized abdominally and the obstructing lesion resected. A new handsewn ileoanal anastomosis was formed. In two cases pouch volume was increased by incorporating an additional loop of ileum. All anastomoses but one were covered by a loop ileostomy. There were no deaths. Major complications occurred in two patients. Function was assessed in 15 patients; in one the ileostomy had not been closed. Median (interquartile range) frequency of defaecation per 24 h fell from 15 (7·3–19·5) to 6 (4·5–6·0) ($P = 0·0033$). Of the 11 patients who required a catheter before operation six evacuated spontaneously, three were improved but intubated on some occasions and two were unchanged after revisional surgery. Of the ten incontinent patients, five became continent, four were improved and one remained unchanged. There was a new continence disturbance in four (minor nocturnal in three) of the remaining five patients. One patient underwent further abdominal salvage surgery and another required establishment of an ileostomy because of poor function. Combined abdominoanal salvage surgery for outlet mechanical obstruction was successful in averting an ileostomy in 13 of 16 patients, and significantly improved pouch function in 12 of 15.

Outlet obstruction is an important cause of dysfunction after restorative proctocolectomy. It may be either functional or mechanical. The latter can be due to stricture of the ileoanal anastomosis, a long efferent ileal limb or a long anorectal stump. Most strictures resolve after dilatation[1,2], but some require corrective surgery. A long anorectal stump is usually associated with a stapled pouch–rectal anastomosis.

While there are several indications for salvage surgery, this report is confined to an analysis of outcome in patients with mechanical outlet obstruction.

Patients and methods

From 1985 to 1994, 16 patients required reoperation by one surgeon (*Table 1*). There were seven women and nine men with a median (interquartile range (i.q.r.)) age of 32 (28·3-41·3) years. Seven patients had been referred. There were nine S, four W, two J, and one H pouch constructions. The original diagnosis was ulcerative colitis in 14 patients and familial adenomatous polyposis in two One patient had had a loop ileostomy raised following a failed attempt at correction of an H pouch that had been malfunctioning for 3 years and has since undergone a second reconstruction. The remaining 15 patients had a functioning pouch before revision surgery. The median (i.q r.) interval between initial pouch construction and abdominal reoperation was 4·9 (2 8–8·3) years. Minimum follow-up after the salvage procedure was 6 months after closure of the ileostomy.

Preoperative clinical details

All patients had severe difficulty in evacuation, requiring catheterization in 11 (*Table 2*). In nine patients with an S pouch this was associated with a long efferent ileal limb. One of these also had a stricture at the ileoanal anastomosis. This patient had an early pouch–vaginal fistula that healed after a drainage procedure. Three of the nine patients also had an efferent limb stricture which rendered intubation of the pouch difficult. In one, histological examination showed ischaemia and the other two had a short stricture at the junction between pouch and efferent limb

Five other patients had tight strictures at the ileoanal anastomosis due to previous anastomotic leakage that had not responded to repeated dilatation (*Fig 1*). One patient with a J pouch and a long rectal stump had a high frequency of defaecation and another had emptying difficulties with a long rectal stump and incompletely divided septum in a J pouch (*Fig 2*).

Ten patients had faecal incontinence (*Table 2*). Six of these leaked during both day and night, and constantly required a pad. Four, including two with a stricture and two with a long efferent limb, leaked only at night.

For 13 patients the reoperation was the first salvage procedure. In three, previous attempts at improving pouch function had failed. One patient had had an efferent limb external prolapse treated by a Marlex (C. R. Bard, Billerica, Massachusetts, USA) pouchopexy and later a transanal resection of the efferent limb. The second had undergone two unsuccessful revisions elsewhere of an H pouch for a strictured ileoanal anastomosis. The third patient had had a transanal resection of part of the efferent limb, without improvement.

Investigations

All patients had endoscopy with biopsy to exclude pouchitis. Pouchography was performed to study pouch size, degree of emptying, length of efferent ileal limb, rectal stump or anastomotic stricture. In patients with an apparently small pouch on contrast radiology or substantial faecal incontinence, physiology studies were carried out to determine pouch volume and compliance, and anal sphincter function

Operation

In 11 patients the pouch was fully mobilized abdominally to the level of the pouch–anal or pouch–rectal anastomosis and the obstructing lesion was resected. In the remaining five cases the stenosed ileoanal anastomosis was excised transanally and a transanal mucosectomy carried out to just above the dentate line. In all cases a new handsewn ileoanal anastomosis to the dentate line was fashioned using interrupted sutures. In all but one patient a protective loop ileostomy was constructed or the previous stoma retained. In all patients the pre-existing pouch

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Table 1 Patient details and indication for surgery

		Before reoperation			After reoperation		
Sex	Indication	24-h frequency	Catheter	Incontinence	24-h frequency	Catheter	Incontinence
M	LEL	24	+	+	6	–	–
M*	LEL	14	+	–	n.a.	n.a.	n.a.
M	LEL	3	+	+	3	–	–
M	LEL	7	+	+	6	–	–
F	LEL	18	+	+	6	–	+
M	LEL	8	+	+	5	+	+
F	LEL	6	+	+	2	+	+
F†	LEL	20	+	+	20	+	+
F	Stricture‡	15	+	–	4	–	+
M	Stricture‡	10	+	–	5	+	+
M	Stricture‡	26	–	+	6	–	–
M	Stricture‡	17	–	+	6	–	–
F	Stricture‡	20	+	+	20	+	+
M	Other§	15	–	–	7	–	+
F	Other#	8	–	–	5	+	–
F	LEL + stricture	4	+	–	4	–	+

*Secondary ileostomy not closed at 2 years. †This patient had formation of permanent ileostomy 9 months later. ‡At the ileoanal anastomosis. §Long rectal stump with J pouch. #Long rectal stump and pouch septum with J pouch. n.a., Not applicable; LEL, long efferent ileal limb of S pouch

Table 2 Pouch function in 15 patients

	Before reoperation	After reoperation	
Catheterization			
Yes	11 (73)	6 spontaneous evacuation	
		3 spontaneous plus intermittent catheterization	
		2 unchanged	
No	4 (27)	3 spontaneous evacuation	
		1 catheter to speed up evacuation at work only	
Incontinence			
Yes	10 (67)		
Day and night	6	4 night only	
		2 none	
Night only	4	3 none	
		1 unchanged	
No	5 (33)	1 continent	
		4 new incontinence	1 one night in two
			2 most nights
			1 day and night

Values in parentheses are percentages

was reanastomosed to the anus at the level of the dentate line or within 1 cm proximally. In two an additional loop of small bowel was incorporated to increase pouch volume.

Results

Surgical complications

There was no operative mortality. Complications occurred in two patients: one developed a leak from the ileoanal anastomosis with a pelvic collection which drained spontaneously transanally. Another had a protracted recovery and needed three further operations: two for recurring small bowel obstruction and one for dehiscence of the abdomen. Fifteen patients subsequently had the ileostomy closed. The patient who had multiple complications still has faecal diversion after 2 years. One of the six patients with a preoperative anastomotic stricture developed a stricture after operation. A new ileoanal stricture occurred in one of the ten other patients and required repeated dilatation under general anaesthesia.

Function

Function was assessed in 15 patients after a median (i.q.r.) of 2·3 (1·5–6·4) years. In the remaining patient the ileostomy was not closed at the time of assessment. Median (i.q.r.) frequency of defaecation fell from 15 (7·3–19·5) to 6 (4·5–6·0) per 24 h ($P = 0{\cdot}0033$, Wilcoxon signed rank test) (*Fig. 3*). Of the 11 patients who required a catheter before operation, six were able to evacuate spontaneously afterwards (*Table 2*). One of these developed a late stricture at the ileoanal anastomosis after 16 months and went back to intermittent catheterization.

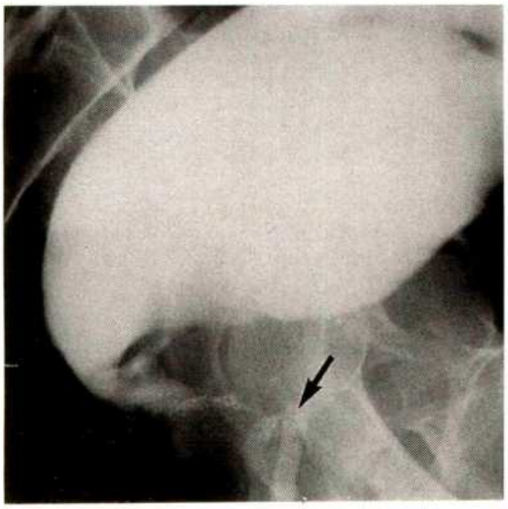

Fig. 1 Long unremitting stricture after stapled ileoanal anastomosis. The tip of the catheter used for instillation of contrast is located at the lower limit of the stricture (arrow)

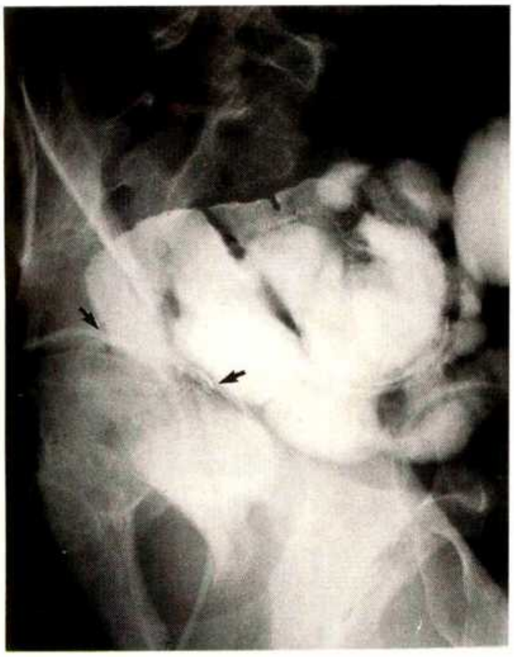

Fig. 2 Retained rectal stump. The pouch was stapled to the rectum (arrows) leaving a stump of approximately 6 cm

Three patients intubated the pouch on some occasions and two were no different after surgery. Of the four patients who did not catheterize before operation one did so afterwards to speed up evacuation at work.

Of ten incontinent patients five became continent, four were improved and one remained unchanged after operation (*Table 2*). Four of the remaining five patients, two men and two women, developed a disturbance of continence after surgery. This was minor in three (night-time seepage), but the fourth patient developed passive leakage during both day and night. This patient developed chronic persisting pouchitis 4 months after ileostomy closure. Only one patient in this group had transanal excision of stricture.

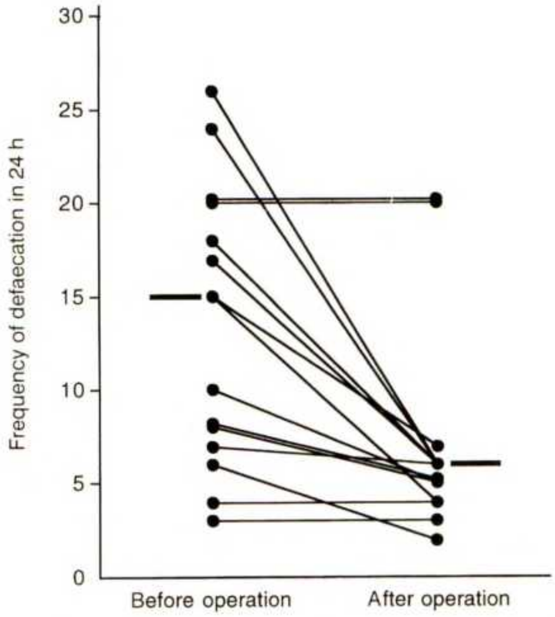

Fig. 3 Frequency of defaecation in 24 h before and after salvage operation in 15 patients. Bars denote median values

Overall outcome

None of the patients had the pouch excised. The patient who experienced multiple complications refused to have the ileostomy closed and still has a loop stoma after 2 years; however, intestinal continuity could be restored. There are two patients who are clinical failures. In one patient urgency and incontinence were improved but high evacuation frequency and dependence on catheterization were not changed; she went on to have a terminal ileostomy performed. The second patient underwent another abdominal salvage operation and is awaiting ileostomy closure. Avoidance of a permanent or long-standing 'temporary' ileostomy was achieved in 13 patients.

Twelve of the 15 patients whose function could be assessed after operation were improved significantly, especially regarding frequency of defaecation. In three patients, evacuation was no better although defaecation frequency was reduced in two.

Discussion

Early interest in restorative proctocolectomy concerned the indications, technique, complications and function[3]. Most patients do well after the operation although long-term failure rates have been reported recently[4]. Some patients have problems that require further surgery to avoid failure and this defines salvage as used in the present report. Patients having salvage operations fall into two groups including those with pelvic sepsis and those with poor function. Poor function may arise for several reasons including pouchitis, outflow obstruction, chronic small bowel obstruction, small bowel motility problems and weak anal sphincter.

Outflow obstruction may be functional or mechanical in origin and the diagnosis needs to be established by formal investigation including evacuation proctography. There are three basic causes for mechanical outflow obstruction. The first is a long efferent ileal limb which occurs especially in S pouches. This type of limb is seen only rarely owing to a trend away from this form of pouch[5]. The second is a long anorectal stump. This is becoming more frequent owing to an increase in stapled pouch–anal anastomosis. While stapling techniques have been described to ensure an anastomosis within the anal canal[6,7], use of the double stapling technique may result in a high anastomosis. The third cause of outflow obstruction is stricture, which is often a sequela of perianastomotic sepsis. Surgery is likely to be effective in mechanical outflow obstruction and the present results confirm this.

Major salvage surgery is indicated in patients who would otherwise require a permanent ileostomy. The patient must be prepared for failure and also made aware that a good functional result cannot be guaranteed. Salvage surgery requires abdominal reoperation and a temporary ileostomy. Total treatment time to closure with definitive function is a minimum of 4–5 months. Some patients may consider that simple removal of the pouch is the better option.

In the selected group of patients reported here the aim of avoiding a permanent or long-term 'temporary' ileostomy was achieved in 12 of 16 patients, with a morbidity rate of 12 per cent. No further complications occurred during subsequent ileostomy closure. This is comparable with reported experience[8].

The high frequency of defaecation was significantly reduced in most patients. Although not improved in some, overall function was better in 12 of 15 patients. In two patients a recurrent stricture at the ileoanal anastomosis was found to explain ongoing evacuation difficulty. In the other no anatomical factor was identifiable.

Others[2] have reported experience of pouch revision for unsatisfactory function in a heterogeneous group of 13 patients with a similarly acceptable morbidity rate. Not all were operated on for outlet obstruction and the moderate results achieved reflect the complexity of the problems. Frequency of defaecation was reduced from 14 to 8 per day and from 3 to 2 per night; satisfactory function was achieved in eight patients.

Minor faecal incontinence, especially night-time soilage, is seen in up to 28 per cent of patients following restorative proctocolectomy[4]. Postoperative maximum resting pressures are significantly lower than those before operation and do not recover in the long term[9]. Even with apparently normal maximum resting pressures large fluctuations in tone have been shown[10]. These indicate internal anal sphincter damage. It has also been demonstrated by prolonged ambulatory manometry that faecal soiling is caused by internal anal sphincter dysfunction and lack of coordination between pouch and anal canal. This may lead to frequent reversal of the pressure gradient between pouch and anal high-pressure zone[11], and is pronounced during sleep when anal resting pressure naturally drops to a low level. Disturbed faecal continence in the presence of anastomotic stricture may be explained by the inability of the muscles to close a rigid, scarred and deformed anal canal. Hence improvement should be expected after debridement of scar tissue and correction of the obstructing lesion.

Salvage surgery for a specific mechanical problem occurring after restorative proctocolectomy is successful in most cases with avoidance of a permanent ileostomy and function acceptable to the patient.

Acknowledgements

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Results from pouch salvage

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Over an 11-year period, 17 salvage procedures were performed on a failed ileal pouch–anal anastomosis carried out for ulcerative colitis from a series of 157 patients. Ten pouches were saved, four excised and three defunctioned. Salvage procedures included five operations for fistulas (three of five successful), six reoperations on the ileoanal anastomosis (five of six successful), three new pouches after previous pouch excision (all failed), and three miscellaneous: excision of an efferent limb (successful), pouchpexy for a pouch prolapse (successful) and postanal repair for incontinence (failed). Pouch salvage may be successful in the motivated patient who wishes to avoid a permanent ileostomy.

Restorative proctocolectomy with ileal pouch–anal anastomosis is considered by many as the procedure of choice for patients with ulcerative colitis, but there is a failure rate of between 6 and 22 per cent[1–3]. As patients usually wish to keep a pouch, despite complications, clinical pressure is high to attempt salvage of the threatened pouch.

This study describes 17 procedures used to salvage an otherwise failed ileoanal pouch given for ulcerative colitis. Patients with familial adenomatous polyposis and functional bowel disease were not included. Pouch salvage is defined as a procedure on the ileoanal anastomosis or the pouch, where pouch excision or permanent defunction was the only other alternative.

Patients and methods

Between February 1983 and May 1994, 157 patients underwent restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) for ulcerative colitis. Seventeen patients presented with complications requiring a salvage procedure. Pouch–cutaneous fistulas except pouch–perineal fistulas are not described here as they have been reported previously[4]. Indications were pouch fistula in five patients (mean 13·8 (range 1–23) months after pouch construction), poor function in two (one long efferent limb and one pouch prolapse), previous proctocolectomy with mucosectomy in three, previous pouch excision in three, previous disconnection of the pouch for sepsis in two, a persistent sinus at the ileoanal anastomosis in one and incontinence in one. There were nine women and eight men (mean age was 34 (range 18–66) years) with J pouches except two with S pouches and two with W pouches. The type of anastomosis was sutured with mucosectomy in four, sutured without mucosectomy in eight and stapled in five. Ten of the 17 patients had a loop ileostomy at the time of pouch construction. The indications for salvage, procedure performed, outcome, follow-up and function are given in *Table 1*. Successful outcome was defined as a pouch in circuit and functional outcome was assessed using a 12-point scoring system[5], which included bowel frequency, soiling, incontinence, wearing of pads, dietary restrictions, use of antidiarrhoeal drugs and urgency. Scores of up to 3 were regarded as 'excellent' outcome, up to 6 as 'acceptable' and more than 6 as 'poor'. In this study, 'excellent' and 'acceptable' outcomes were grouped together as 'good' outcome. The score was obtained by a postal questionnaire and all casenotes were carefully reviewed.

Results

The results are given in *Table 1*. The mean follow-up since salvage procedure for the ten functioning pouches was 30·6 (range 7–84) months. Further details are presented in three groups: five patients with a fistula, nine who underwent reoperation on the ileoanal anastomosis (including three new pouches) and three patients with miscellaneous reasons for salvage.

Salvage for fistula

The first four fistulas were suprasphincteric, and the patients presented 2–4 months after closure of the ileostomy (one patient had no ileostomy but was defunctioned when the fistula first became apparent 1 month after the pouch construction). The patient with a rectovaginal fistula proved to have a fistula between a heavily inflamed rectal remnant and the vagina.

Salvage involving the ileoanal anastomosis

The three completely new pouches (J pouch with handsewn ileoanal anastomosis) were constructed 16–26 months after failure of a primary pouch operation. One of them was excised because of chronic pelvic sepsis and stenosis at the ileoanal anastomosis resulting in intolerable function. The other two needed defunctioning 2 and 3 months after initial closure of the ileostomy because of difficulty in pouch evacuation, megapouch and ileoanal stenosis.

It was possible to construct a pouch with a handsewn ileoanal anastomosis despite severe pelvic fibrosis in all three patients referred after previous proctocolectomy and mucosectomy.

The mucosal advancement flap was performed 3 years after pouch construction with a covering ileostomy for a persisting sinus at the ileoanal anastomosis which was covered by a pouch advancement flap.

In one of the patients with dehiscence of the ileoanal anastomosis, the associated sepsis was drained and a new anastomosis fashioned at the same time. Recurrent sepsis necessitated disconnection, and the pouch was brought up as an end ileostomy. In the other patient, the pouch was

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Table 1 Indication for salvage and operation performed with outcome, follow-up and function

Sex	Reason for salvage procedure	Operation details	Salvaged?	Follow-up since salvage or time until excision (months)	Function
Salvage for fistula					
F	Pouch–vaginal fistula	Seton fistulotomy with partial division of external sphincter	Yes	54	Poor
F	Pouch–vaginal fistula	Seton fistulotomy with partial division of external sphincter	Yes	24	Poor
F	Pouch–perineal fistula	Seton fistulotomy with sphincter reconstruction	No: pouch excised Developed long ileoanal stricture	88	n a
M	Pouch–perineal fistula	Seton fistulotomy, pelvic sepsis	No: refistulation, excised for poor function	17	n.a.
F	Rectovaginal fistula with pelvic abscess	Residual diseased rectum and fistula excised, sutured pouch–anal anastomosis	Yes	48	Good
Salvage involving the ileoanal anastomosis					
F	Previous pouch ischaemic, excised	New pouch from ileum, sutured anastomosis	Defunctioned for ileoanal stenosis	8	n.a
M	Previous pouch excised for sepsis	New pouch from ileum, sutured anastomosis	Defunctioned for ileoanal stenosis	7	n.a.
F	Previous pouch ischaemic, excised	New pouch from ileum, sutured anastomosis	No: pouch excised for poor function	12	n a
M	Previous mucosectomy	Routine pouch, sutured anastomosis, stenosed pelvic floor	Yes	14	Poor
M	Previous mucosectomy	Routine pouch, sutured anastomosis, stenosed pelvic floor	Yes	10	Poor
F	Previous mucosectomy	Routine pouch, sutured anastomosis, stenosed pelvic floor	Yes	10	Poor
F	Persistent defect, ileoanal anastomosis	Mucosal advancement flap over sinus	Yes	7	Good
M	Ileoanal dehiscence, pelvic sepsis, pouch disconnected	Pouch reconnected to anal canal, sutured	Yes	48	Good
M	Pelvic sepsis with ileoanal dehiscence	Disconnection of pouch, drainage of pelvic sepsis, neo-ileoanal anastomosis	No: recurrent pelvic sepsis, pouch disconnected	2·5	n.a.
Salvage for miscellaneous reasons					
M	Long efferent limb causing intolerable diarrhoea	Excision of efferent limb and new stapled ileoanal anastomosis	Yes	84	Poor
M	Prolapse of pouch	Pouchpexy	Yes	7	Good
F	Incontinence	Postanal repair	No: pouch excised Problem: long efferent S limb	22	n.a.

Seventeen salvage procedures were performed: ten pouches were saved, four excised and three defunctioned. n.a., Not applicable

brought up as a stoma initially, and 8 months later reanastomosed with excellent functional result.

Miscellaneous reasons for salvage

One S pouch with a long efferent limb causing intolerable diarrhoea and impaired evacuation 2 years after pouch construction was converted into a J pouch by resection of the efferent limb. Six years later, pouch function was poor, but Crohn's disease was identified (for the first time) in the resected efferent limb.

A complete pouch prolapse presented with mucous discharge and incomplete evacuation 7 years after pouch construction (W pouch) which could be demonstrated only under general anaesthetic.

Postanal repair was performed 4 months after S pouch construction for incontinence without any benefit. At pouch excision 2 years later, a long efferent limb of the S pouch was noted which was almost certainly responsible for the poor function. This could have been excised, but the patient was not prepared to consider a further salvage procedure.

Discussion

The widespread acceptance of IPAA as the treatment of choice for ulcerative colitis means that the management of complications may become common as patients are reluctant to lose continence. Although in ten of 17 patients the pouch remained in circuit, six had rather poor function. All but one were satisfied with the outcome and would not revert to an ileostomy.

Fistulas complicating pouch surgery have been managed with variable success[4,6,7]. Treatment of the two pouch–vaginal and two pouch–perineal fistulas involved interference with the sphincter mechanism. After pouch construction both resting and squeeze anal pressures fall below preoperative levels[8,9]. This decrease may be caused by division of autonomic nerves at the site of transection of the gut or by damage to the external or internal sphincter during rectal excision. Further interference with the sphincter mechanism may lead to imperfect continence. A previous review reported a high success rate for pouch construction after previous anal surgery, even in one patient who had undergone proctocolectomy with intersphincteric dissection[10]. All pouches constructed after previous mucosectomy were functioning, but defaecation frequency remained high and all had soiling, presumably because the internal sphincter was compromised. In patients with anastomotic dehiscence and pelvic sepsis it seems prudent to allow the sepsis to settle before subsequent reconnection as suggested by Fleshman *et al.*[11]. Delayed pouch–anal anastomosis could lead to pelvic fibrosis making subsequent reconstruction even more difficult[12].

Outcome for the three patients with new pouches constructed after previous pouch excision was disappointing: none were functioning. Wexner *et al.*[6] described one redo pouch for anovaginal fistula, and Galandiuk *et al.*[13] reported one redo pouch for sepsis and four for unsatisfactory function but with no mention of individual functional outcome. Poggioli *et al.*[12] described one redo pouch for sepsis, with a good functional result. In the present series the three patients with redo pouch procedures had considerable pelvic fibrosis and had already lost at least 40 cm of terminal ileum. If the new pouch fails, they are at risk of losing up to 100 cm of small bowel. The new anastomoses seem to develop some stenosis and, even if there is no mechanical obstruction, the bowel proximal to the anastomosis dilates with features of malabsorption and bacterial overgrowth leading to megaloblastic anaemia and chronic abdominal distension.

Salvage surgery on a long efferent limb has been reported previously with varying success[13,14]. The patient in the present series had Crohn's disease which is usually associated with a poor functional outcome due to chronic pouchitis and small bowel strictures[15].

The single patient with pouch prolapse (treated by 'pouchpexy') raises the question as to whether pouches should be fixed routinely in the pelvis.

Incontinence procedures after pouch construction probably have a place provided that the underlying cause is firmly established. In one patient a long efferent limb of the S pouch was responsible for incontinence rather than an impaired sphincter mechanism. In two patients with incontinence after IPAA for megarectum (not presented here) it has been possible to restore continence by means of a pelvic floor repair.

Salvage surgery after IPAA is probably worthwhile. Treatment of low fistulas which involve the sphincter mechanism may result in soiling. IPAA after proctocolectomy with mucosectomy is technically possible, but the patient should be warned that function may not be perfect. Completely new pouches produce disappointing results. The success rate of pouch salvage may approach 60 per cent, which may be acceptable for the motivated patient who prefers an imperfect functioning ileoanal pouch over an ileostomy.

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Local recurrence following total mesorectal excision for rectal cancer

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Early results after rectal cancer surgery in a defined population were compared before and after the introduction of total mesorectal excision. In the first period (1984–1986) 211 cases of rectal cancer were diagnosed and in the second (1990–1992) 230. Of these, 134 patients in the first period (group 1) had anterior resection or abdominoperineal excision which was considered curative. In the second period 128 curative anterior resections and abdominoperineal excisions were performed by a limited number of surgeons familiar with total mesorectal excision (group 2). No differences between the groups were found in stage distribution, rate of curative operations, postoperative complications or postoperative mortality. Local recurrence had developed in 19 patients in group 1 and in eight in group 2, 1 year after the end of the study periods ($P = 0.03$). Local radicality was in doubt in 13 patients in group 1 and in eight in group 2. In the remaining 121 and 120 patients, 13 and four local recurrences respectively were present ($P = 0.03$). Actuarial analysis showed a significant reduction in local recurrence rate ($P = 0.03$) and an increase in crude survival ($P = 0.03$) at 4 years in group 2 compared with group 1. Total mesorectal excision reduces the local recurrence rate after excision of rectal cancer.

Local recurrence after surgery for rectal cancer is a disaster for the patient. In addition to severe pain, there may be interference with circulation and nerve function of the legs, ureteric obstruction, intestinal obstruction, fistulation, infection and discharge. Cure at this stage is seldom possible and the disease often takes a prolonged and excruciating course. Palliative treatment is not always successful and may in addition have severe side-effects.

Local recurrence rates show considerable variation in different series and can be regarded as an indicator of the quality of the surgical treatment, although differences may exist regarding the definition of a curative operation. The technique of total mesorectal excision is claimed substantially to reduce local recurrence rates and, in single-surgeon series, a local recurrence rate below 10 per cent after curative anterior resection has been reported[1–5]. In contrast, some population-based studies[6–8] have found local recurrence rates of 40 per cent and higher. In randomized trials of adjuvant therapy, local recurrence rates of 25–35 per cent have been observed in control groups. Adjuvant radiotherapy with or without chemotherapy has reduced these rates to approximately half of that[9–12]. No data have been published, however, demonstrating that radiotherapy has any additional effect in series with local recurrence rates below 10 per cent with surgery alone.

It is difficult to randomize between different surgical techniques, but comparison of data obtained during time periods when different surgical techniques were used may be meaningful, provided there is no selection bias and no change in classification or follow-up, as pointed out by Fielding[13]. In the county of Östergötland, Sweden, a computerized system for registration and follow-up of all cases of colorectal cancer has been in use since 1984. In a study of the cases from 1984 to 1986[14] the local recurrence rate was found to be 22 per cent 5 years after curative operation. In an attempt to improve those results, three of the surgical departments late in 1989 adopted the technique of total mesorectal excision described by Heald[15].

The aim of this study was to compare postoperative complications, mortality and local recurrence for patients treated between 1984 and 1986 with those treated between 1990 and 1992 by surgeons familiar with total mesorectal excision.

Patients and methods

The numbers of patients with rectal cancer recorded from 1984 to 1986 and from 1990 to 1992 were 211 and 230 respectively. The population in the catchment area averaged 370 000 persons in both periods, and few patients were treated in hospitals outside the area. Between 1984 and 1986 this was the case for only four patients with colorectal cancer.

Apart from 12 patients with typical clinical or radiological findings, all had histologically proven adenocarcinoma diagnosed by the surgeon responsible for the treatment as 154A (rectosigmoid junction) or 154B (rectal ampulla) according to the *International Classification of Diseases*, ninth revision.

Total mesorectal excision involved excision of all mesorectal tissue in tumours situated in the middle or lower part of the rectum. For lesions located in the upper rectum, however, all mesorectal tissue down to at least 5 cm below the tumour was excised. The technique of total mesorectal excision also involved careful and precise dissection in anatomical planes laterally and anteriorly. The technique is more demanding than traditional dissection and a limited number of surgeons in each department was familiar with the technique – altogether eight surgeons. Since 1989 an effort has been made to concentrate patients with rectal cancer to these surgeons, but no other changes have been made deliberately. Curative resection implied a resection with no residual macroscopic tumour, free margins including perirectal margins on routine microscopic examination and no evidence of distant metastasis. Curative resection was locally radical. When either the surgeon or pathologist was in doubt about local radicality, resection was classified as of doubtful local radicality. When both surgeon and pathologist were in doubt, the operation was deemed palliative. Perforation of the tumour or bowel wall during surgery had no influence on the decision as to whether the operation should be locally radical or not. Staging was done according to Dukes classification[16] with an added 'D'-stage for patients with metastases or locally not radically resected disease. Patients in stage 'D' with all evident metastases resected were considered to have had curative treatment. The degree of differentiation was classified as poor, intermediate or high.

Follow-up was not standardized, but was performed mainly in the surgical outpatient clinic, and similarly during the two

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periods. Diagnosis of recurrence was made on clinical grounds but whenever possible verified with biopsy or cytological examination. When not known, the cause of death was taken from the death certificate.

Preoperative radiotherapy as adjuvant treatment to surgery was used for one patient in the first period and for three in the second. Chemotherapy was not used as an adjuvant during the study periods.

Patients having anterior resection or abdominoperineal excision considered curative between 1984 and 1986 formed group 1. Group 2 comprised the same category of patients treated between 1990 and 1992 by surgeons familiar with total mesorectal excision (*Fig. 1*). In the first period six abdominoperineal excisions and in the second three anterior resections and two abdominoperineal excisions were classified as palliative without metastasis. In three of these cases in the second period both the surgeon and pathologist considered the resection as of doubtful local radicality. The local recurrence and survival rates in group 1 at 31 December 1987 were compared with those in group 2 at 31 December 1993.

Survival and local recurrence rates were also calculated by means of the actuarial method[17]. For comparison between groups the log rank method[18] was used. $P<0.05$ was considered significant in two-tailed tests.

Results

Characteristics of the patients and tumours in the two groups are shown in *Table 1*. The distance between the anal verge and the distal border of the tumour is shown in *Fig. 2*. No differences were found between the groups in the rate of curative operation or stage distribution. In *Table 2* surgical details are shown. There were no differences in complication or postoperative mortality rates (*Table 3*). In each group three patients died more than 30 days after surgery from complications. In group 1 no postoperative deaths were due to anastomotic leakage but in group 2 two were caused by leakage; neither patient had a protecting stoma.

The local recurrence rate in group 1 1 year after the study period was 19 (14 per cent) of 134 cases, nine (12 per cent) following anterior resection and ten (17 per cent) following abdominoperineal excision (*P* not significant). In *Fig. 3* the distance from the anal verge is shown for the tumours that recurred locally. No correlation was found between local recurrence rate and distance from the anal verge. Of 121 operations with local radicality, 15 local recurrences (12 per cent) were found; two of these were re-resected with curative intent and the patients were free from local recurrence on 31 December 1987, giving a local recurrence rate of 11 per cent (13 of 121). In the 13 cases with doubtful local radicality four local recurrences were found. At 5 years 25 local recurrences (19 per cent) were diagnosed in group 1, including new local recurrences in the re-resected patients.

Local recurrence appeared in group 2 1 year after the study period in eight (6 per cent) of 128 patients. Of 120 cases with local radicality, five local recurrences (4 per cent) were found; one of these patients was re-resected with curative intent and was free from local recurrence on

Table 1 Details of patients and tumours

	Group 1	Group 2
No. of patients	134	128
Median (range) age (years)	71 (41–93)	70 (36–93)
Sex ratio (M:F)	80:54	75:53
Dukes stage*		
A	36 (27)	31 (24)
B	43 (32)	46 (36)
C	51 (38)	49 (38)
'D'	4 (3)	2 (2)
Degree of differentiation*		
High	8 (6)	6 (5)
Intermediate	103 (77)	104 (81)
Poor	22 (16)	15 (12)
Not known	1 (1)	3 (2)

*Values in parentheses are percentages

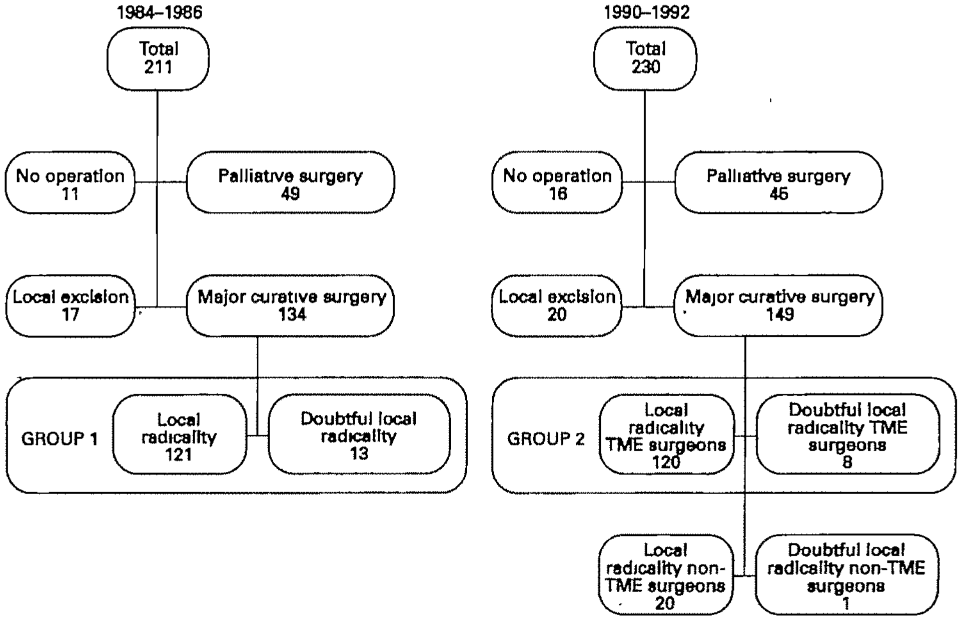

1984–1986
Total 211
No operation 11
Palliative surgery 49
Local excision 17
Major curative surgery 134
GROUP 1
Local radicality 121
Doubtful local radicality 13
1990–1992
Total 230
No operation 16
Palliative surgery 45
Local excision 20
Major curative surgery 149
GROUP 2
Local radicality TME surgeons 120
Doubtful local radicality TME surgeons 8
Local radicality non-TME surgeons 20
Doubtful local radicality non-TME surgeons 1

Fig. 1 Management of all patients presenting with rectal cancer in 1984–1986 and 1990–1992, and definition of groups 1 and 2. TME surgeon, surgeon familiar with total mesorectal excision

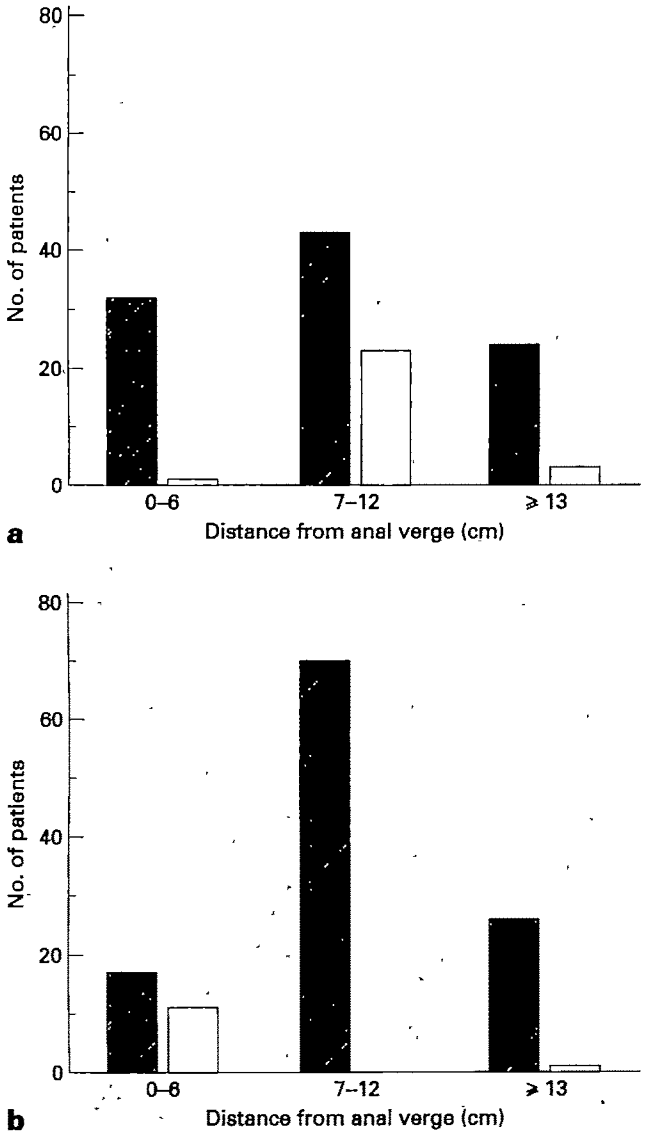


Fig. 2 Distance from the anal verge to the distal border of the tumour in a group 1 (data missing in eight patients) and b group 2 (data missing in three). ■, anterior resection; □, abdominoperineal excision

Table 2 Surgical details

	Group 1 ($n = 134$)	Group 2 ($n = 128$)
Resection	74 (55)	110 (86)
Perforation*	9 (12)	6 (5)
Contamination†	9 (12)	8 (7)
Stapled	60 (81)	94 (85)
Protective stoma	11 (15)	63 (57)
Rectal washout	43 (58)	93 (85)
Total mesorectal excision	0 (0)	67 (61)
Abdominoperineal excision	60 (48)	18 (14)
Perforation*	23 (38)	3 (17)
Contamination†	6 (10)	2 (11)
Total mesorectal excision	0 (0)	17 (94)

Values in parentheses are percentages. *Perforation of tumour or adjacent bowel wall during surgery. †Faecal contamination

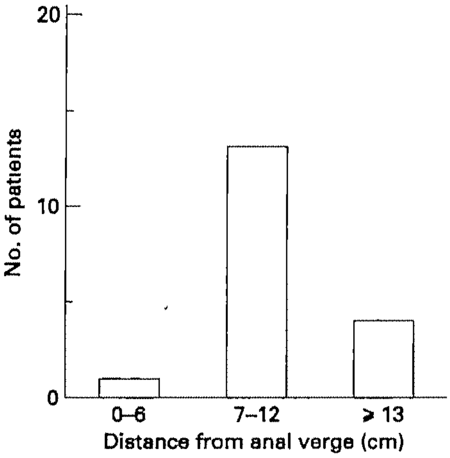


Fig. 3 Distance from the anal verge to the distal border of the tumour in patients in group 1 with local recurrence (data missing in one patient)

Table 3 Postoperative complications

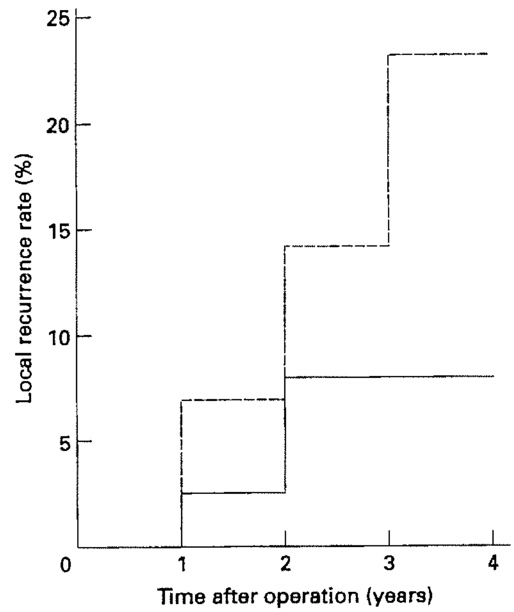
	Group 1 ($n = 134$)	Group 2 ($n = 128$)
Anastomotic leakage	7 (9)*	8 (8)*
Stomal complications	7 (9)*	4 (5)*
Wound infection	14 (10)	15 (12)
Severe infection	14 (10)	6 (5)
Thromboembolic complications	2 (1)	1 (1)
Other complications	29 (22)	33 (26)
Death within 30 days	3 (2)	3 (2)
No. of patients with complications	60 (45)	48 (38)

Values in parentheses are percentages. *Percentage of patients with anastomosis or stoma

31 December 1993, giving a local recurrence rate of 3 per cent (four of 120). One of the patients with local recurrence had preoperative adjuvant radiotherapy. Of the eight cases with doubtful local radicality in group 2, three local recurrences were found. Of the eight patients in group 2 with local recurrence, three did not undergo total mesorectal excision (one locally radical surgery, two doubtful local radicality). The difference in local recurrence rate was significantly lower in group 2 1 year after the end of the study periods, both after all curative resections ($P = 0{\cdot}03$) and after locally radical resections ($P = 0{\cdot}03$).

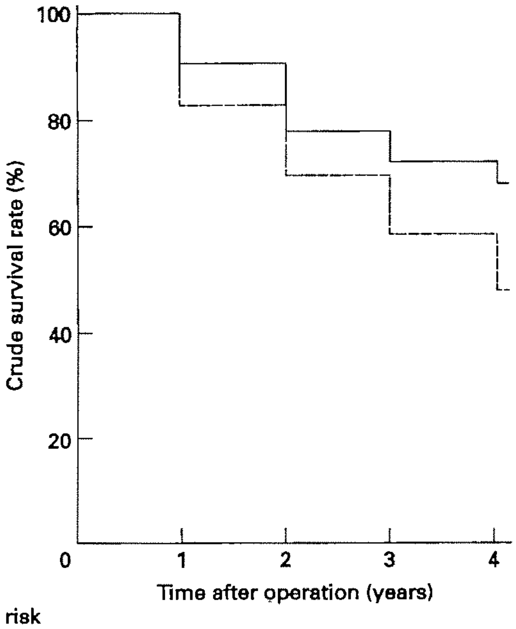
Local recurrence rates up to 4 years, calculated by the actuarial method, are shown in *Fig. 4* for groups 1 and 2. Patients who died within 30 days of operation were not included. The log rank test showed a significant reduction in local recurrence rate in group 2 ($P = 0{\cdot}03$).

In group 1 the mortality rate from all causes 1 year after the end of the study period was 35 per cent and that of patients with known cancer was 25 per cent. In group 2 the corresponding mortality rates were 23 and 15 per cent respectively. Crude survival up to 4 years (including postoperative deaths) calculated by the actuarial method is shown in *Fig. 5*. The log rank test showed a significant increase in the crude survival rate in group 2 ($P = 0{\cdot}03$). There was no difference in local recurrence or survival rates between participating hospitals.



No. at risk	0	1	2	3	4
Group 1	131	102	53	22	0
Group 2	125	112	60	25	0

Fig. 4 Actuarial analysis of local recurrence. Postoperative deaths within 30 days were excluded. -----, Group 1; ———, group 2. $P = 0{\cdot}03$ (log rank test)



No. at risk	0	1	2	3	4
Group 1	134	108	55	26	0
Group 2	128	114	64	27	0

Fig. 5 Actuarial analysis of crude survival. Postoperative deaths were included. ----, Group 1; ———, group 2 $P = 0{\cdot}03$ (log rank test)

Of the 21 anterior resections and abdominoperineal excisions performed by surgeons not familiar with total mesorectal excision in the second period, local recurrence was found in four patients (19 per cent), all after locally radical operations. Median age of patients in this group was 70 years and the stage distribution was 38 per cent for A, 24 per cent for B and 38 per cent for C. No patient had adjuvant radiotherapy.

Discussion

This study compared two periods, 1984–1986 and 1990–1992, from the same hospitals and catchment areas, and included all patients with rectal cancer. The period from 1987 to 1989 was excluded because of a trial with preoperative adjuvant radiotherapy in the three hospitals[19] and because total mesorectal excision was introduced in 1989. In spite of this, the time periods are sufficiently close to avoid significant changes in perioperative and anaesthetic conditions. Apart from the change in surgical technique, there has been a trend towards more anterior resections and fewer abdominoperineal excisions. There was also a limitation of the number of surgeons treating patients with rectal cancer within the departments of surgery. In other respects the periods were comparable. In the first period a small difference was found in the local recurrence rate between abdominoperineal excision and anterior resection. This difference disappeared if only cases with local radicality were considered and therefore the trend towards more anterior resections in group 2 did not seem to explain the difference in local recurrence rate between the two groups.

The major difference in group 2 was the effort made to achieve greater lateral clearance and total mesorectal excision. Altogether, eight surgeons were familiar with the technique of total mesorectal excision, although it was not always used for technical reasons or for tumours situated in the upper part of the rectum. This modest concentration of surgery is, however, unlikely to explain the reduced local recurrence rate in group 2, since eight surgeons treating 128 cases over 3 years gives an average of only about five cases per surgeon per year. Twenty-one (14 per cent) of 149 curative anterior resections and abdominoperineal excisions in the second period were performed by other surgeons. The local recurrence rate among those patients was similar to that in group 1.

The mean follow-up time was 2·5 years, which may be too short to draw firm conclusions. There is, however, a strong tendency towards a substantial reduction in local recurrence rate for surgeons using total mesorectal excision that cannot be explained by selection of cases, changes in classification or a single surgeon's exceptional personal skill. Another recent series has shown a similar low rate of local recurrence after mesorectal excision[20].

The technique of total mesorectal excision has enforced the trend towards low anterior resection[5,21], but it has also increased the need for a temporary protective stoma. Although the postoperative clinical anastomotic leak rate and postoperative mortality due to complications showed no significant differences between the periods, three patients died (two after curative resection, one after palliative resection) as a result of anastomotic leakage in the second period. None of these patients had a protective stoma. This is in agreement with other studies[22,23] and, in the authors' opinion, a protective stoma is required after low anterior resection with total mesorectal excision and a conventional straight anastomosis unless there is good reason to omit the stoma.

In the present study patients with irresectable metastases were not included in the calculations of local recurrence. Patients with metastases seldom live long enough to develop local recurrence, and to include them would give a falsely low local recurrence rate. The small group of patients with doubtful local radicality included those with fixed or perforated tumours which could be removed with no obvious macroscopic tumour left behind. These cases are difficult to classify and would in many series be classified as palliative, hence they are shown separately. Such patients would probably benefit from adjuvant radiotherapy, but since identification is made during or after operation radiotherapy has to be given after surgery. However, when the local recurrence rate after surgery alone stays below 10 per cent, routine adjuvant radiotherapy to all patients seems to be of limited value.

The survival rate after total mesorectal excision is claimed to be higher than after conventional surgery, with or without adjuvant chemotherapy[24]. In the present study a significantly improved crude survival rate was found in patients in group 2, but longer follow-up is necessary before definitive conclusions can be drawn.

A system for routine quality assurance is necessary to recognize complications and to detect inferior results early, in order to ensure optimal surgical treatment. In Östergötland a computerized system for prospective registration of all patients with colorectal cancer has been in use for 10 years. It provides data on surgical procedures, postoperative complications and follow-up. The results from each surgical department can thus be compared with those of the whole county. Using this quality assurance system, the present study has shown that total mesorectal excision can be performed by a number of surgeons working in different hospitals, with good results.

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Randomized controlled trial of lateral internal sphincterotomy with haemorrhoidectomy

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A prospective trial was conducted to compare haemorrhoidectomy alone (control, group 1) with haemorrhoidectomy plus lateral internal sphincterotomy (group 2) for prolapsed piles. Some 33 patients (18 men, 15 women) of mean(s.e.m.) age 40(2·3) years were randomized, 16 to group 1 and 17 to group 2. There were no significant differences in postoperative pain scores. Mean resting and maximum anal squeeze pressures, studied 6 weeks and 3 months after operation, were generally lower in group 2, but were not significantly different. Two patients in group 2 were distressed by incontinence to liquid faeces which persisted in one after 1 year. There were no other complications in either group after a mean(s.e.m.) follow-up of 11(0·4) months. The addition of lateral internal sphincterotomy to routine haemorrhoidectomy is unnecessary and carries the added risk of incontinence.

Haemorrhoidectomy is effective in treating prolapsed piles. The addition of lateral internal sphincterotomy[1,2] might help to treat the presumed internal anal sphincter spasm and reduce postoperative pain[3]. The clinical benefits and physiological consequences of performing this procedure for uncomplicated piles require further clarification.

Patients and methods

This was a controlled randomized prospective study comparing patients treated either by haemorrhoidectomy and lateral internal sphincterotomy or by haemorrhoidectomy alone (controls) Postoperative pain, clinical outcome and anal manometry findings were studied. Thirty-three consecutive patients with three symptomatic prolapsed haemorrhoids (large haemorrhoids tending to be permanently prolapsed) who underwent elective surgery over an 8-month period (March to November 1994) consented to recruitment. There were 18 men and 15 women of mean(s.e.m.) age 40(2·3) years. The mean(s.e.m.) duration of symptoms was 61(10) months. Eight patients had fresh rectal bleeding as well as prolapsed piles. The patients had a mean(s.e.m.) of 1(0·1) bowel motions a day. Before surgery routine clinical examination and rigid proctoscopy were performed to exclude other colorectal pathology

Surgery

The operation was performed under general anaesthesia in 11 patients and caudal anaesthesia in 22. All patients had complete excision of three haemorrhoids by a single surgeon (Y H.H) using a diathermy method described previously[4,5]. There was no preceding anal dilatation. The base of the pile was removed without ligation of the pedicle and haemostasis was secured by diathermy.

Sixteen of the patients were randomized by sealed envelope to have no further procedure (controls, group 1). The remaining 17 patients had lateral internal sphincterotomy (group 2) This was performed in the left haemorrhoidectomy wound, up to the dentate line. There was a good match with regard to age, sex and method of anaesthesia in both groups

Wounds were left open to granulate, and none had dressings applied into the anal canal. Routine bulk laxatives were prescribed and patients were given on-demand oral ketoprofen 100 mg twice daily as required, or intramuscular pethidine 1 mg per kg body-weight. All patients had a bowel motion before discharge on the second postoperative day.

Clinical assessment

Pain score was assessed with a linear analogue scale by an independent observer (B C.O.), blinded to the randomization: zero represented no pain and 100 the worst pain ever experienced. The pain score was taken at 4 and 24 h after surgery. Pain score at defaecation and maximum postoperative pain were also recorded Patients were questioned about continence at 3-monthly follow-up

Anorectal physiology

Anorectal manometry was performed with a perfusion system (Synectics, Stockholm, Sweden). Measurements were taken before operation, at 6 weeks and at 3 months after surgery

Statistical analysis was done with the Mann–Whitney U and χ^2 tests, as appropriate.

Results

Clinical

There were no significant differences in the pain scores between groups 1 and 2 (*Table 1*), or between patients who received general or caudal anaesthesia. Two patients from group 2 (both men), but none from group 1, reported occasional incontinence to liquid stools 3 months after surgery. This persisted in one patient after 1 year of follow-up. The trial was stopped after this because incontinence did not occur in controls or in the authors' previous experience with haemorrhoidectomy alone. There were no other complications, including haemorrhage, anal stricture or urinary retention, in either group. No recurrences occurred in either group after a mean(s.e.m.) follow-up of 11(0·4) months.

Anorectal physiology

Mean resting pressure (*Fig. 1*) and maximum squeeze pressure (*Fig. 2*) were generally lower after surgery with lateral internal sphincterotomy, but were not statistically significant.

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Table 1 Pain score in patients after haemorrhoidectomy with and without lateral internal sphincterotomy

	Controls ($n = 16$)	Lateral internal sphincterotomy ($n = 17$)	P†
Postoperative pain score*			
At 4 h	40 (0–70)	15 (0–50)	0·6
At 24 h	30 (30–35)	20 (0–55)	0·3
Pain score at first defaecation*	70 (40–70)	67·5 (20–80)	0·2
Maximum postoperative pain score*	40 (25–70)	60 (30–80)	0·2
Pethidine injection requirements (1 mg/kg body-weight)	1 (0–2)	0 (0–2)	0·6
Ketoprofen requirements (100-mg tablets)	0·5 (0–2)	0 (0–3)	0·4

Values are median (range). *Pain score: 0, no pain; 100, worst pain ever experienced. †χ^2 test

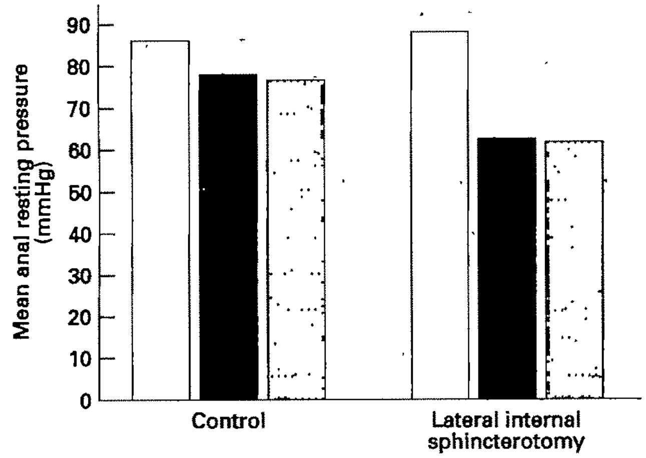

Fig. 1 Mean resting anal pressure after haemorrhoidectomy without (control) and with lateral internal sphincterotomy. □, Before operation; ■, 6 weeks after operation; □, 3 months after operation. The Mann–Whitney U test showed no significant differences between the two groups

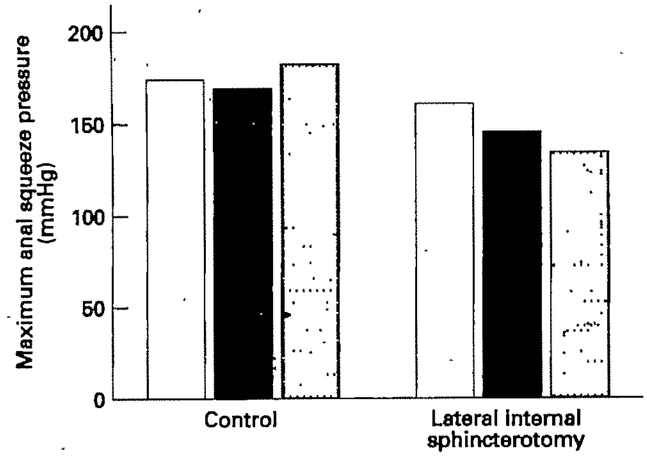

Fig. 2 Maximum anal squeeze pressure after haemorrhoidectomy without (control) and with lateral internal sphincterotomy. □, Before operation; ■, 6 weeks after operation; □, 3 months after operation. The Mann–Whitney U test showed no significant differences between the two groups

Discussion

Lateral internal sphincterotomy and anal dilatation have been considered in the treatment of haemorrhoids because of the raised anal pressures in this condition[6,7]. The increased pressure was attributed to hypertrophy of the internal anal sphincter[8,9], and lateral internal sphincterotomy was directed towards this[10,11]. It has recently been argued that the raised anal pressures result primarily from hypertension in the vascular anal cushions. These pressures normalize after removal of the haemorrhoidal anal cushions[12]. The vascular anal cushions have been measured directly and found to be hypertensive in piles[13]. The results of haemorrhoidectomy are superior to those of lateral internal sphincterotomy alone for piles[14,15]. Measures to weaken the anal sphincter in addition to haemorrhoidectomy appear unnecessary, and the addition of anal dilatation to haemorrhoidectomy does not improve the cure rate[16]. There were no recurrences after haemorrhoidectomy alone in the present patients after a mean follow-up of 11 months.

The pain score and analgesic requirements were similar in patients who had haemorrhoidectomy plus sphincterotomy. This included an assessment during defaecation, when anal sphincter spasm was expected to have maximal effect in causing postoperative pain. Anal dilatation also appears to have only a mininal effect on reducing postoperative pain[17]. These findings suggest either that internal sphincter spasm is not important in contributing to pain or that the pain is adequately controlled by routine analgesia alone. However, it is acknowledged that posthaemorrhoidectomy pain may sometimes increase after day 3, and this aspect was not assessed in the present study. Pain may also be affected by personality, anxiety and depression.

The addition of lateral internal sphincterotomy to haemorrhoidectomy resulted in generally lower postoperative anal pressures, but the difference was not significant. However, two patients having sphincterotomy became incontinent to liquid faeces. This had not occurred in control patients or in the authors' previous experience of haemorrhoidectomy alone[5]. The incontinence could not be predicted by anal pressures measured before or after operation. This incontinence was similar to the results of anal dilatation plus haemorrhoidectomy[16]. Anal dilatation is discouraged in recent clinical reports[18], and endosonographic studies confirm extensive fragmentation of the internal anal sphincter[19]. Although lateral internal sphincterotomy may be justifiable in the presence of coexisting anal fissure[20], use of the procedure in addition to routine haemorrhoidectomy is not required as it carries the added risk of incontinence. An alternative might be to use chemical agents such as topical glyceryl trinitrate to reduce the tone of the anal sphincter temporarily[21].

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Surgical workshop

Technique for full-thickness muscle closure of laparoscopic port sites

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Since the introduction of laparoscopic surgery there have been several case reports of incisional hernia at sites where laparoscopic trocars have been inserted through the abdominal wall[1–5]. These occur predominantly through port sites with a diameter of 10 mm or more, either through the linea alba at the umbilicus, or through more lateral defects. Fascial closure reduces the incidence but does not eliminate hernias entirely as they can occur into the subfascial space[1,2]. As complex laparoscopic surgery involving the use of several large ports becomes increasingly common, the incidence of this complication is likely to increase. The authors believe it is important to perform a full-thickness closure of all muscle defects 10 mm or greater in diameter.

Surgical technique

The straight needle on a suture (2-0 polyglactin) is passed up the shaft of a dismantled Veress needle, leaving about 4 cm of suture protruding. Avoiding the skin, this assembly is used to pass the thread through the muscle layers on one side of the cannula (*Fig. 1a*). By withdrawing the Veress needle slightly, a loop of thread is conveniently offered to a grasping forceps within the abdomen. This thread is transferred to a forceps within the cannula to be withdrawn and the suture is brought out through that cannula. The Veress needle is then removed from the suture completely. Where the port passes obliquely through the abdominal wall this initial manoeuvre is performed along the upper aspect of the port (*Fig. 1a*).

With the cannula held at right angles to the skin, the straight needle on the other end is used to perform the same manoeuvre diametrically opposite (*Fig. 1b*). The needle is cut off and the cannula is withdrawn over the suture (*Fig. 1c*), which is tied leaving the knot on the inside. Any subcutaneous tissue caught in the suture can be freed bluntly by a finger at this point to prevent unsightly dimpling of the overlying skin.

This method produces a reliable gas-tight closure allowing the pneumoperitoneum to be maintained while each port is closed. When closing the second to last 10-mm port, the cannula is left in place and the laparoscope is passed down it alongside the suture to visualize closure of the final site.

Discussion

This technique, even in the most obese patient in whom effective closure is otherwise impossible, allows straightforward rapid full-thickness muscle closure of all laparoscopic port sites. No special instruments are required, the cost is that of a single suture and a variety of suture materials is available. The possibility of incorporating bowel into the closure[2] is avoided by visualizing placement of each stitch.

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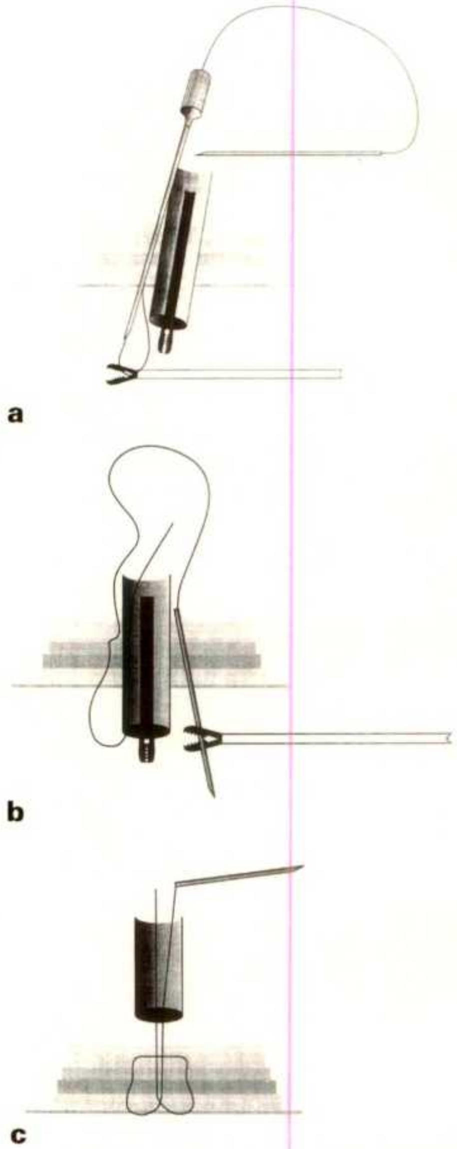

Fig. 1 Schematic representation of this technique for full-thickness muscle closure of laparoscopic ports. See text for full explanation

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Anatomical basis of autonomic nerve-preserving total mesorectal excision for rectal cancer

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Total mesorectal excision with autonomic nerve preservation for rectal cancer is based on the anatomy of the mesorectum and of the pelvic autonomic nerves. Cadaver dissections were performed to describe the relationship between these structures. Between the rectum and the sacrum a retrorectal space can be developed, lined anteriorly by the visceral leaf and posteriorly by the parietal leaf of the pelvic fascia. The hypogastric nerve runs anterior to the visceral fascia, from the sacral promontory in a laterocaudad direction. The splanchnic sacral nerves originate from the sacral foramina, posterior to the parietal fascia, and run caudad, laterally and anteriorly. After piercing the parietal layer of the pelvic fascia, approximately 4 cm from the midline, the sacral nerves run between a double layer of the visceral part of the pelvic fascia. The relationship between the hypogastric nerves, the splanchnic nerves and the pelvic fascia was comparable in all six specimens examined.

Conventional low anterior and abdominoperineal resections for rectal cancer are associated with a significant incidence of sexual[1–6] and urinary[7–10] morbidity. The presumed mechanism for sexual and urinary dysfunction is damage to the pelvic autonomic parasympathetic and/or sympathetic nerves during surgery. These injuries are most commonly related to blunt dissection or to the degree of lateral dissection. In total mesorectal excision the rectum is mobilized circumferentially using sharp dissection under direct vision along the parietal pelvic fascia[11–13]. This technique, together with an awareness of the pelvic autonomic nerve pathways, makes it possible to identify and preserve the pelvic autonomic nerves, therefore minimizing sexual and urinary dysfunction[13].

The anatomy of the parietal and visceral pelvic fascia[14–20], as well as that of the sacral (parasympathetic contribution) nerves and the sympathetic hypogastric nerves, has been described previously[14,21–24]. However, the relationships between the autonomic nerves and the pelvic fascia, especially in the area of the so-called 'lateral ligaments', remains unclear from these studies. A better understanding of the relationships of the 'lateral ligaments', the pelvic fascia and the autonomic nerves will facilitate mesorectal excision as well as autonomic nerve preservation in the treatment of rectal cancer. Cadaver dissections were performed to study these anatomical relationships.

Patients and methods

The pelves of three female and three male cadavers were dissected. Preservation was performed by the injection of embalming fluid in the femoral artery. All specimens were initially hemisected in the mid-sagittal plane, without damaging the retrorectal anatomy. Various stages of each dissection were recorded photographically.

Results

A space posterior to the perirectal fat and anterior to the pelvic wall, the retrorectal space, can be developed after mid-sagittal hemisection (*Fig. 1*). This space is lined with two layers of pelvic fascia: the parietal fascia on the posterior (sacral) side and the visceral fascia on the anterior (rectal) side. The two fasciae are connected to each other by a layer of loose connective tissue. The perirectal fat within the visceral fascia is referred to as the mesorectum. Both the visceral and parietal fasciae are thin; however, they can be separated from the pelvic wall or from the mesorectal fat quite easily. The parietal fascia covers the muscles of the pelvic side walls (piriformis, coccygeal and levator ani muscles) and the anterior surface of the sacrum and coccyx. Anterior to the sacrum, the parietal fascia can be difficult to separate as in some locations the fascia is fused to the periosteum.

The retrorectal space is defined laterally by the internal iliac arteries and veins, and caudally by the anal sphincters. At the lateral borders of the retrorectal space, as in the distal midline posteriorly, the visceral fascia becomes continuous with the parietal fascia. Some inconsequential branches of the internal iliac veins and the presacral venous plexus cross the retrorectal space.

Anterior to the fourth sacral vertebra, the two fasciae are strongly connected by a dense band of fibres: the rectosacral fascia (*Fig. 1*). As the rectosacral fascia extends laterally to the lateral border of the retrorectal space, it becomes a thin and sometimes transparent structure 1·5–2 cm from the midline. Caudal from the rectosacral fascia, the visceral fascia is a bilayered structure, with an anterior and a posterior leaf (*Fig. 2*).

The hypogastric nerves are identified at the sacral promontory, approximately 1 cm lateral to the midline and 2 cm median to each ureter. The hypogastric nerve lies posterior to the peritoneum and directly anterior to the visceral fascia. In thin specimens the hypogastric nerve lies directly posterior to the peritoneum as well. The hypogastric nerve continues caudal and laterally, following

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the course of the ureter and the internal iliac artery along the pelvic wall (*Figs 2* and *3*).

The splanchnic branches of the sacral nerves may be identified at the sacral foramina (*Fig. 4*). Splanchnic branches from the third and fourth sacral root were present in all specimens. In one specimen, a splanchnic branch from the second sacral nerve was identified. The third sacral nerve was the largest one in all specimens. The splanchnic nerves run laterocaudad and anteriorly along the pelvic wall over the piriformis muscle. From the sacral foramina to a point approximately 3 cm more

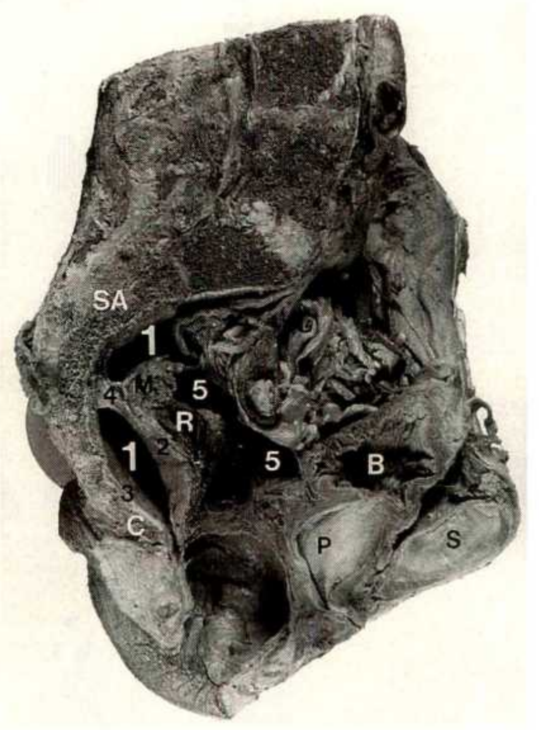

Fig. 1 Mid-sagittal hemisection of a male pelvis. 1, Retrorectal space; 2, visceral fascia; 3, parietal fascia; 4, rectosacral fascia; 5, peritoneal cavity; R, rectum; M, mesorectum; B, bladder; P, prostate; S, symphysis pubis; SA, sacrum; C, coccyx

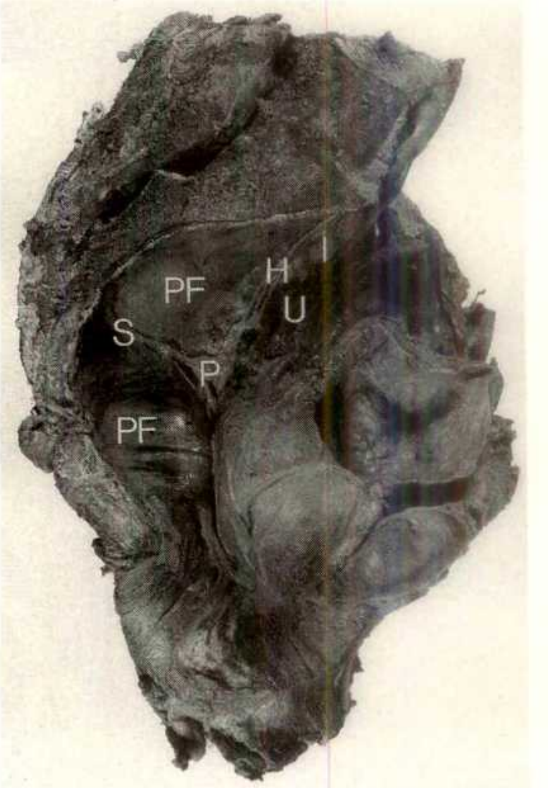

Fig. 3 Mid-sagittal hemisection of a male pelvis after removal of the rectum and mesorectum. H, hypogastric nerve; S, sacral splanchnic nerves; P, pelvic autonomic nerve plexus; PF, parietal fascia; I, internal iliac artery; U, ureter

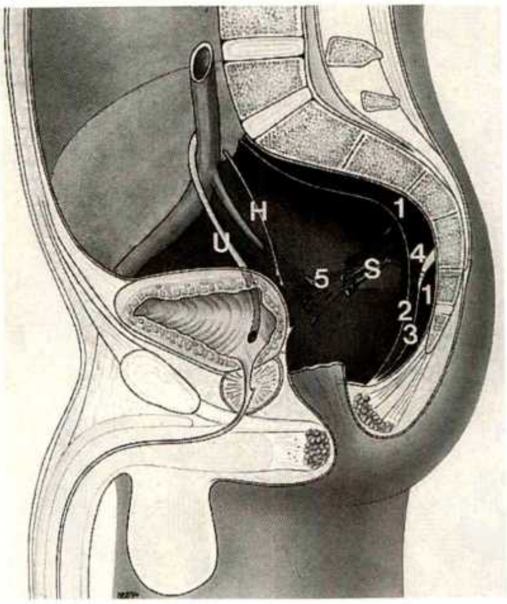

Fig. 2 Schematic drawing of the relationship between the pelvic autonomic nerves and the pelvic fasciae. 1, Retrorectal space; 2, anterior leaf of visceral fascia; 3, posterior leaf of visceral fascia; 4, rectosacral fascia; 5, middle rectal artery; S, sacral splanchnic nerves; H, hypogastric nerve; U, ureter

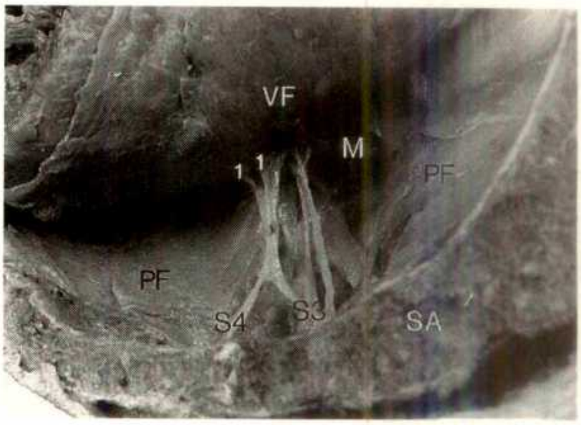

Fig. 4 Detail of the sacral splanchnic nerve, dissected from the parietal fascia. S3, third sacral splanchnic nerve; S4, fourth sacral splanchnic nerve; 1, medial splanchnic branches (to rectum); M, middle rectal vein; VF, visceral fascia; PF, parietal fascia; SA, sacrum

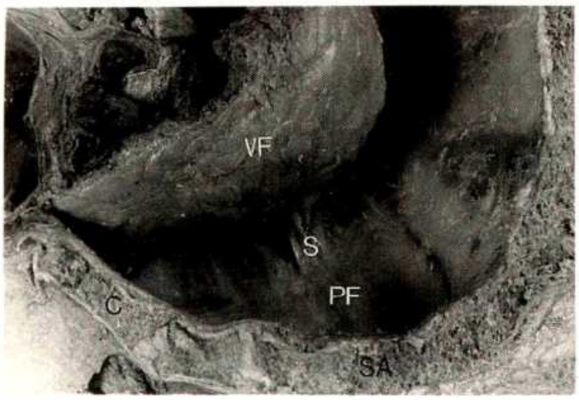

Fig. 5 Detail of the retrorectal space with the rectosacral fascia removed and sacral splanchnic nerves covered by parietal fascia. S, sacral splanchnic nerves; VF, visceral fascia; PF, parietal fascia; SA, sacrum; C, coccyx

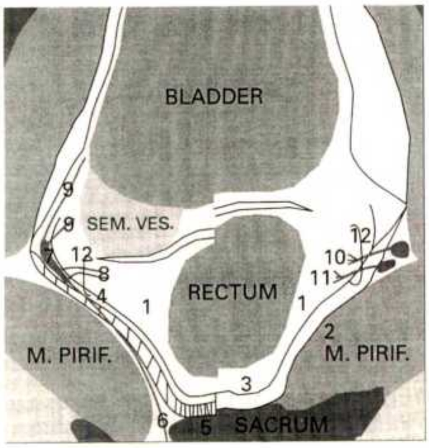

Fig. 6 Diagram of an oblique transverse section of the pelvis, posteriorly at the level of S3 and anteriorly at the level of the pubic symphysis. The right half of the drawing is at a level 2 cm higher than the left half of the drawing. M. PIRIF., piriform muscle; SEM. VES., seminal vesicle; 1, mesorectum; 2, parietal fascia; 3, visceral fascia; 4, anterior and posterior leaf of the visceral fascia; 5, rectosacral fascia; 6, sacral splanchnic nerve; 7, pelvic autonomic nerve plexus; 8, mesorectal nerve branches; 9, urogenital nerve branches; 10, middle rectal artery; 11, middle rectal vein; 12, 'lateral ligament'

lateral, the splanchnic nerves are covered by the parietal fascia (*Fig. 5*). To enter the visceral compartment the nerves then pierce the parietal fascia and continue central to the parietal fascia, between the posterior (outer) and anterior (inner) leaves of the visceral fascia caudad to the rectosacral fascia. Where the splanchnic nerve crosses from the parietal to the visceral compartment, the splanchnic nerves are always ensheathed by fascia. As they enter the visceral compartment, small branches from the splanchnic nerves can be identified running medially, entering the mesorectum. These branches constitute the specific parasympathetic nerve supply of the rectum. However, most fibres of the splanchnic nerve continue to the anterior visceral compartment, i.e. the genitourinary organs (*Figs 2* and *4*).

The hypogastric nerve and the sacral splanchnic nerves join laterally on the pelvic wall to form the pelvic autonomic nerve plexus. The pelvic autonomic nerve plexus is a rhomboid plaque of nervous tissue (*Fig. 3*). Branches to the genitourinary organs originate from the pelvic autonomic nerve plexus.

The middle rectal artery and vein were identified in all specimens. In two specimens the middle rectal artery was only an insignificant branch. The middle rectal artery and vein are branches of the pudendal artery and vein, and originate just cranially from the prostate in men and from the vaginal fornix in women, just superior to the rectosacral fascia. The origin of the middle rectal artery is lateral to the origin of the middle rectal vein. The retrorectal space extends just lateral to the pudendal artery. Therefore, the middle rectal artery and vein have to cross the retrorectal space to reach the mesorectum. Branches of the middle rectal artery and vein run medially towards the rectum and pierce the visceral fascia about 4 cm from the midline. In all specimens the middle rectal artery and vein crossed the splanchnic branch of the third sacral nerve cranially (*Figs 2* and *4*). In the specimen where a splanchnic branch of the second sacral root could be identified, this branch crossed the middle rectal artery and vein cranially. All nerves and vessels are embedded in fat and fibrous tissue. When the mesorectum is pulled medially, the complex of middle rectal artery and vein with the sacral nerves resembles the form of a 'ligament' extending from the pelvic wall to the mesorectum. Nevertheless, no ligament *per se* exists in the absence of surgical dissection (*Fig. 6*).

Discussion

In this study the anatomical relationships of the retrorectal pelvic fascia, the pelvic autonomic nerves and the middle rectal artery are described. The dissections demonstrate that the anatomical organization of the retrorectal area is similar in six specimens. A detailed knowledge of this anatomy is helpful for total mesorectal excision with autonomic nerve preservation for rectal cancer.

The fascial lining which envelopes the mesorectum and the rectum is referred to as the visceral fascia[14–16]. Fritsch[25,26] showed that the visceral fascia develops from a condensed band of mesenchymal tissue, the rectal adventitia. Several authors have confirmed the finding that the visceral fascia forms a 'hammock' between the left and right internal iliac arteries, suspending the rectum with its perirectal fat[14,16–18,20]. The loose connective tissue between the visceral and parietal fascia gives the rectum some mobility, allowing the rectum to straighten during defaecation.

The rectosacral fascia has been previously described by Crapp and Cuthbertson[19] and by Sato and Sato[27]. The probable role of the rectosacral fascia is to anchor the rectum to the sacral curvature, preventing rectal prolapse[19]. The rectosacral fascia may play an important role in the outcome of surgery for rectal cancer. During conventional surgery, which is performed with blunt dissection, the rectum is mobilized by entering the hand in the presacral space, when the rectosacral fascia will be encountered. If the rectosacral fascia is pushed bluntly, avulsion of the fascia from the sacrum may occur, causing bleeding from the presacral venous plexus. In an attempt to avoid avulsion injury to the presacral vessels the dissecting hand may naturally shift forward, inadvertently entering the mesorectum. In this manner, conventional blunt dissection may lead to inadequate resection of mesorectal tissue distal to the rectosacral fascia. Sharp division of the rectosacral fascia ensures an intact mesorectum and a bloodless dissection through the retrorectal space.

The finding that in all specimens splanchnic branches of the third and fourth root were present is in concordance with studies of Schlyvitsch and Kosintzev[21] and of Harman[28]. Harman[28] also supports the finding that the third sacral root is the major contributor. Beyond the rectosacral fascia, i.e. S4, the visceral fascia is composed of two leaves. This double layer of visceral fascia forms a funnel for the splanchnic nerves on their way to the bladder, prostate and penis in men and to the bladder, clitoris, labia and vagina in women. The splanchnic nerves enter this funnel immediately they pierce the parietal fascia. In this way the splanchnic nerves cross the retrorectal space but are always covered by elements of the visceral fasciae. Roberts and Taylor's description[29] of the pathway of the splanchnic nerve between the two leaves of 'presacral fascia' is compatible with the present findings. Waldeyer[14], who gave a detailed description of the pelvic autonomic nerves, stated that branches of the splanchnic nerve are ensheathed by extensions of the parietal and visceral fasciae on their way to the pelvic organs. Wilson[17] describes the splanchnic nerves as travelling through the visceral fascia. During nerve-sparing surgery for rectal cancer, the double layer of visceral fascia is not easily recognized.

The hypogastric nerve does not cross the retrorectal space since it enters the pelvis within the visceral compartment. To spare the hypogastric nerve during total mesorectal excision, a step in dissection level has to be made just medial to the nerves. Posterior and lateral to the hypogastric nerves the visceral fascia remains attached to the pelvic wall, while the visceral fascia medial to the left and right of the hypogastric nerves will be resected.

The middle rectal artery was identified in all specimens, although it was a very small branch in two. The literature is not consistent on the presence of the middle rectal artery. Widmer[30] found a middle rectal artery in 50 (64 per cent) of 78 pelvic halves; the mean diameter of the artery was 0·5 mm and the median was less than 0·5 mm. Boxall *et al.*[31] found a middle rectal artery in 61 (95 per cent) of 64 pelvic halves. Sato and Sato[27] reported a middle rectal artery in 18 (22 per cent) of 81 pelvic halves; the mean diameter of the artery was 1·6 mm. Ayoub[32], who excluded middle rectal arteries with a diameter of less than 1 mm, reported the presence of the artery in only seven (8 per cent) of 84 pelvic halves. These variations may be explained by differences in considering the smallest branches as arteries. Arterial branches with a diameter of less than 0·5 mm may be regarded as arterioles and have no surgical significance. The middle rectal artery invariably runs superior to the third sacral nerve. This makes it a useful landmark for identifying this nerve after the middle rectal artery is identified, or vice versa.

Several authors have described the 'lateral ligament' as a structure extending from the (meso)rectum to the pelvic side wall[13,20,33]. During the present dissections no circumscribed structure was found that could be defined as the lateral ligament. Rather, when the mesorectum is pulled medially, the complex of middle rectal artery and vein, the splanchnic nerves entering the mesorectum, and most importantly their accompanying connective tissue, form a bandlike structure extending from the lateral pelvic wall to the mesorectum. The splanchnic nerves and the pelvic autonomic nerve plexus are particularly prone to injury when this structure is divided during surgery (*Fig. 6*).

The relationship between the hypogastric nerves, the splanchnic nerves, the middle rectal artery and the pelvic fascial planes were comparable in all six dissected specimens. A detailed knowledge of this anatomy makes it possible to perform *en bloc* resection of the rectum with its complete mesorectum while sparing the autonomic nerves

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Laser Doppler blood flow measurement in rectal resection for carcinoma – comparison between the straight and colonic J pouch reconstruction

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Lower rates of anastomotic leakage have been reported after rectal resection with a colonic pouch–anal anastomosis than with a conventional straight anastomosis. The microcirculation in the bowel segment that was used for construction of a colonic pouch or a conventional straight anastomosis was examined. Transmural colonic blood flow was measured by laser Doppler flowmetry during the operation before the construction of a straight ($n = 16$) or pouch ($n = 14$) anastomosis. The blood flow recordings were first done before dissection of the bowel at one point close to the planned bowel end and at another point 8 cm more proximally. A second recording was done at the same sites after dissection and, where appropriate, after construction of the pouch, but before the anastomosis was completed. In the straight group (end-to-end anastomosis), blood flow levels at the site intended for the anastomosis were significantly decreased following dissection of the bowel. In the pouch group (side-to-end anastomosis), blood flow levels at the site of the anastomosis were similar following dissection of the bowel and pouch construction. It is concluded that unaffected blood flow at the site of the anastomosis of the pouch may be a favourable factor for anastomotic healing.

Total mesorectal excision is currently widely accepted as a standard procedure to obtain local radicality in surgery for rectal cancer. When a sphincter-saving procedure is appropriate the rectum is transected at the levator plane irrespective of the tumour level, and the anastomosis will be constructed 4–6 cm from the anal verge. It is generally recognized that, during the first year after such a low sphincter-saving resection of the rectum, patients usually experience a varying degree of poor bowel function. Urgency, frequent bowel movements and occasional incontinence can be related to loss of the rectal reservoir and a reduced resting anal pressure[1]. Consequently a colonic pouch has been used to improve bowel function by increasing the reservoir function of the 'neorectum'[2,3].

The most significant early complication after a low sphincter-saving resection is anastomotic leakage, which is regarded as a difficult problem to prevent[4]. The incidence of symptomatic leakage after a low stapled straight anastomosis, regardless of the use of a temporary stoma, generally ranges from 5 to 15 per cent[4–6], and was even higher in earlier series[7]. In contrast to this, leakage rates in series with a colonic J pouch reconstruction appear to be less than 5 per cent[8–10]. One aspect of the surgical technique is that the straight reconstruction has an end-to-end anastomosis whereas the pouch has a side-to-end anastomosis. Adequate blood supply is of fundamental importance in the healing of anastomoses. The aim of this study was, therefore, to investigate whether there is any difference in the microcirculation at the site of the anastomosis between the two methods of reconstruction.

Patients and methods

Patients

The colonic blood flow was measured by laser Doppler flowmetry in 30 patients during low anterior resection for carcinoma (*Table 1*). Twenty-five of the 30 patients were part of a randomized trial designed to evaluate bowel function in patients with a colonic pouch in comparison with the conventional straight reconstruction. The trial was approved by the ethics committee at the University Hospital in Linkoping in 1990. There was no difference in age or sex distribution, operating time, perioperative blood loss or the method of anaesthesia. Epidural anaesthesia was not used nor did any patient receive steroid treatment. None had diabetes. Two patients had preoperative radiotherapy (25 Gy during 1 week before the operation).

Laser Doppler method

The working principle of laser Doppler flowmetry has previously been described in detail[11]. In this study we used the laser Doppler system (Periflux, PF1d, serial number 164, gain setting 10, time constant 3 s, frequency limit 12 kHz, Perimed, Stockholm, Sweden) which has previously been used for calibration of the flowmeter signal in absolute flow units in the human colon[12]. Recordings were made with a probe with a measuring depth of about 6 mm in bowel wall, that is transmural in the human colon[13]. The probe had one emitting and two receiving fibres with a fibre diameter of 0·7 mm and fibre separation of 0·7 mm. The instrument set-up has been used in clinical studies of intestinal microcirculation[14].

Table 1 Characteristics of 30 patients

	Straight ($n = 16$)	Pouch ($n = 14$)
Sex ratio (F:M)	7:9	5:9
Age (years)	74 (37–82)	68 (40–77)
Tumour height above anal verge (cm)	9 (6–12)	8 (4–11)
Anastomotic height above anal verge (cm)	5 (3–6)	4 (2·5–5)
Part of colon used for reconstruction (sigmoid:descending)	10:6	7:7
Operating time (min)	192 (140–260)	210 (160–250)
Operative blood loss (ml)	300 (150–900)	325 (150–800)

Values are expressed as median (range) unless otherwise stated

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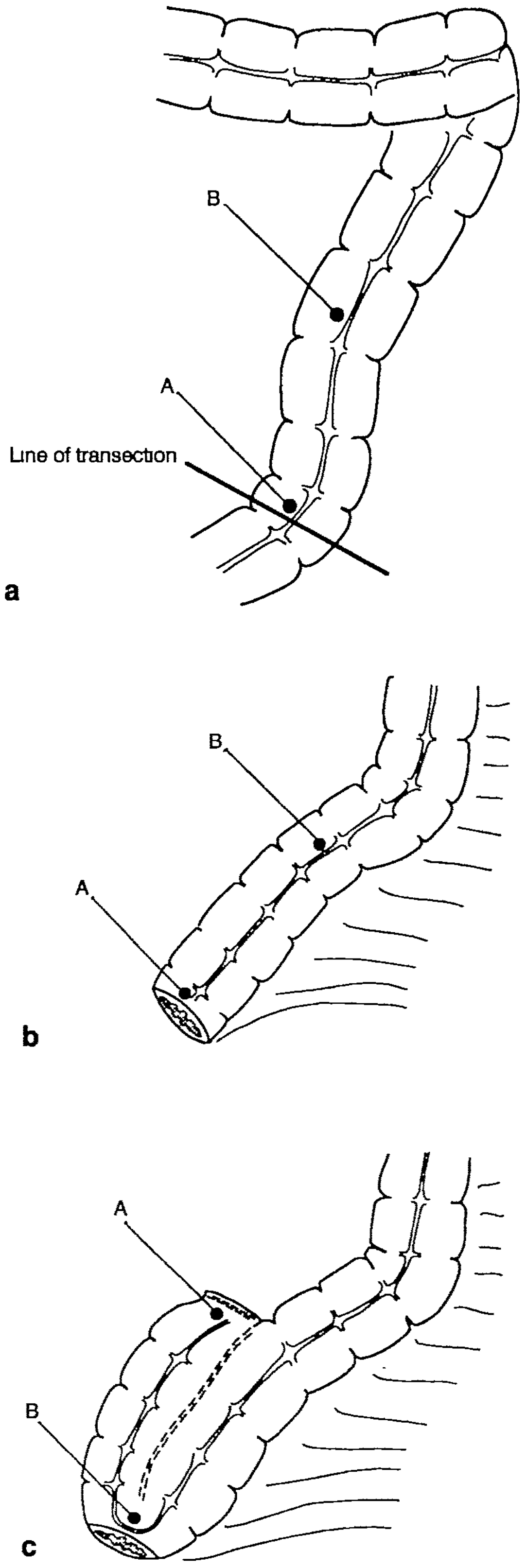

Fig. 1 Sites of laser Doppler blood flow measurements in the left colon. a Before any dissection of the bowel: site A denotes the intended bowel end and site B the bowel side, 8 cm proximal to A b After dissection of the bowel in patients with the straight reconstruction. c In patients with a colonic pouch the site of the anastomosis in the pouch group is at the apex of the pouch, site B

Operative technique

A standardized rectal dissection following the principle of total mesorectal excision[15] was done in all patients. The level of transection of the distal bowel was determined by the mesorectal excision rather than by the height of the tumour, thus leading to an anastomosis at the top of the anal canal in most patients. The proximal sigmoid was used for the reconstruction in 17 patients (straight, $n = 10$; pouch, $n = 7$), leaving the left colic vessels intact. In the remaining 13 patients (straight, $n = 6$, pouch, $n = 7$) the inferior mesenteric vessels were divided at their origin, the splenic flexure was mobilized and the descending colon was used for the reconstruction. The same double stapling technique[16] was used for the anastomosis either with a straight colonic end ($n = 16$) or a colonic pouch ($n = 14$). The colonic J pouch, 7–8 cm in length, was made by folding the colon and creating a side-to-side anastomosis with a stapler introduced through the apex of the pouch. A temporary loop ileostomy was used in all patients.

Laser Doppler measurements

Blood flow recordings were done in all patients at two sites on the colon before any dissection or preparation of the bowel was started. The proximal level of transection of the colon was decided and blood flow recordings were made antimesenterically close to the planned bowel end (site A) and 8 cm more proximally (site B) (*Fig. 1*). A second set of recordings was made at the same sites after the specimen had been removed, the mesentery had been divided, and immediately before the anastomosis in the pelvis was completed. The second set of recordings was made in the straight group after the bowel end was transected and prepared for the anastomosis and in the pouch group after the pouch was constructed (*Fig. 1*). Site A (the bowel end) was used for the anastomosis in the straight group and site B (the side) for the anastomosis in the pouch group. It was not, however, possible to reach the anastomosis deep in the pelvis to make additional measurements from the serosal side after the anastomosis was completed. The laser Doppler probe was held manually without pressure against the serosa, avoiding the taenia of the colon. Triplicate recordings were obtained from steady tracings lasting for at least 20 s at each site of measurement. Blood flow values were given in relative flow units (V).

Statistical analysis

The Wilcoxon signed tank test was used as the data of the blood flow measurements were not normally distributed (Shapiro–Wilks test for normality). Values are presented as median (interquartile range (i.q.r.)) unless otherwise stated. $P < 0{\cdot}05$ was considered significant in a two-tailed test.

Results

Blood flow levels in the unprepared colon (median (i.q.r.) 17·3 (14·5–21·0) V in all sites together) were similar in both groups and similar to the results from earlier clinical studies with the same instrument set-up[14]. The blood flow levels obtained before and after bowel preparation according to the type of reconstruction (straight or pouch) are shown in *Table 2*. At the bowel end the blood flow was significantly lower following bowel preparation in both the straight group ($P = 0{\cdot}016$) and in the pouch group ($P = 0{\cdot}019$). At the bowel side, 8 cm proximal to the bowel end, the blood flow levels were not significantly changed after bowel preparation (straight group, $P = 0{\cdot}70$; pouch group, $P = 0{\cdot}19$). The blood flow values according to the level of bowel division (descending or sigmoid) are shown in *Table 3*. There was a significant drop in blood flow at the bowel end in both the descending ($P = 0{\cdot}020$) and the sigmoid ($P = 0{\cdot}019$) colon. At the bowel side flow was

Table 2 Blood flow levels (V) according to type of reconstruction

	Bowel end (site a)		Bowel side (site b)	
	Straight*	Pouch	Straight	Pouch*
Before dissection	18·3 (13·7–21·7)	16·5 (14·3–23·5)	19·0 (15·0–22·0)	17·0 (14·4–19·5)
After dissection (after pouching construction in applicable patients)	13·5 (11·3–17·7)	14·2 (11·5–17·7)	17·8(13·6–22·9)	16·7 (11·0–21·3)
P†	0·016	0·019	0·70	0·19

Values are expressed as median (interquartile range) Straight anastomosis, $n = 16$, pouch anastomosis, $n = 14$ *Site used for the anastomosis to the top of the anal canal in each group. †Wilcoxon signed rank test

Table 3 Blood flow levels (V) according to level of bowel division

	Bowel end		Bowel side (8 cm proximal to the bowel end)	
	Descending	Sigmoid	Descending	Sigmoid
Before dissection	17·7 (14·5–24·0)	16·0 (13·8–20·3)	19·0 (14·8–22·8)	17·0 (14·6–19·0)
After dissection (after pouch construction in applicable patients)	16·6 (11·5–18·0)	13·0 (11·0–16·8)	19·0 (13·0–22·5)	17·3 (12·8–20·0)
P*	0·020	0·019	0·27	0·72

Values are expressed as median (interquartile range). Descending colon, $n = 13$, sigmoid colon, $n = 17$. *Wilcoxon signed rank test

unaffected by the extent of dissection in both the descending ($P = 0·27$) and the sigmoid ($P = 0·72$) colon.

One patient in the straight anastomosis group had an anastomotic leak and subsequently an anastomotic stricture despite an anastomotic blood flow that was close to the median value for the group The stricture was successfully dilated with a balloon.

Discussion

The principle of a side anastomosis in gastrointestinal surgery is well recognized. It is a standard technique for oesophagojejunal anastomoses but is much less used in colorectal surgery. It is of interest that, in a retrospective study[17], the leak rate was only 4 per cent with the side-to-end colorectal anastomosis described by Baker[18] in 1950 compared with 23 per cent in the conventional end-to-end anastomosis.

Comparisons of leak rates from different series are difficult to interpret and experience with the colonic pouch is still limited. The rationale for this study was the reported difference in anastomotic leakage between the straight and pouch reconstruction[4–10].

The laser Doppler technique was used to measure blood flow because it provides a tool for continuous recording of the transmural microcirculation and the measurement can be repeated during operation. It is unlikely that the blood supply at the top of the anal canal is the critical factor[7]; therefore the blood supply to the proximal, that is the colonic, part of the anastomosis was focused upon.

In the straight group, significantly lower blood flow levels were found at the site intended for the anastomosis after bowel dissection compared with the reference levels before dissection. In the pouch group, the blood flow levels at the site of the anastomosis, that is 8 cm proximal to the bowel end, were unchanged following bowel dissection and construction of the pouch. Decreased flux levels at the bowel end after dissection were also found when the results were analysed according to whether the descending or the sigmoid colon was used for the reconstruction.

The decreased blood flow at the bowel end after preparation, despite an intact mesentery, is similar to the findings in experiments with dogs after transection of the bowel and different lengths of devascularization[19]. In another study in patients, however, it was shown that the tissue oxygen tension increased in the descending colon after dissection and high ligation of the inferior mesenteric vessels[20]. The reason for the differing results is unclear but laser Doppler flowmetry cannot be directly compared with oxygenation measurement unless both methods are used in the same study. Construction of the pouch by folding the colon and creating a 7–8-cm side-to-side anastomosis did not seem to impair further the blood flow at the bowel end, which is encouraging with regard to pouch construction.

The results demonstrate, however, adequate blood flow levels at the anastomosis in both groups. The levels following bowel preparation are well above any critical level for bowel wall integrity[21]. However, the subsequent circular stapling can lead to a further decrease of staple-line blood flow[22], and occasional drops in systemic blood pressure during the recovery phase after surgery may lead to critical levels in blood flow at the anastomosis[23].

It is concluded that blood flow seemed unaffected at the site of the anastomosis of the pouch, whereas the colonic end in the straight coloanal anastomosis is more liable to become relatively ischaemic This may be a favourable factor for anastomotic healing in the colonic J pouch type of reconstruction.

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Short note

Removal of circulating cytokines by continuous haemofiltration in patients with systemic inflammatory response syndrome or multiple organ dysfunction syndrome

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High continuous levels of plasma circulating cytokines have been reported in patients with systemic inflammatory response syndrome (SIRS)[1]. Such patients either produce excessive amounts of cytokines or cannot clear them from the circulation, and have been suggested to be at an increased risk of developing multiple organ dysfunction syndrome (MODS)[2]. In this context, cytokine removal may prevent the development of MODS. A study was therefore made of the effects of continuous haemofiltration (CHF) on blood levels of circulating cytokines and on pulmonary, cardiovascular or renal function in patients with SIRS or MODS.

Patients and methods

Six patients of mean(s.e.m.) age 51(7) years were studied. The causes of SIRS were acute pancreatitis, sepsis following enteric perforation, sepsis following traumatic liver injury and multiple blood transfusions for haemorrhagic shock due to multiple trauma. CHF was initiated when signs of SIRS or multiple organ dysfunction developed despite surgical, antimicrobial or supportive therapy. The first session of CHF was conducted over 24 h[3]. It was followed by a mean 24-h control period before a second session of haemofiltration. Measurements were performed before and after each filtration session.

Results

The first session of CHF reduced the mean(s.e.m.) level of plasma interleukin (IL) 6 and IL-8 from 1769·7(1186·3) to 284·3(210·3) pg/ml and from 604·8(551·4) to 57·5(26·0) pg/ml respectively. This was associated with a mean(s.e.m.) increase in urinary flow from 67(18) to 150(71) ml/h, mean arterial blood pressure from 93(7) to 110(9) mmHg, systemic vascular resistance index from 108·4(20·2) to 175·3(34·3) kPa s per l per m² and the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (P_{aO_2}/F_{iO_2}) from 28·0(2·3) to 37·0(3·7) kPa. Accordingly, intravenous fluid volume, the dose of vasoactive amines and F_{iO_2} were reduced.

In the control period, a rebound rise of plasma IL-6 or IL-8 was noted in four patients, associated with decreases in urinary flow, mean arterial blood pressure, systemic vascular resistance index or P_{aO_2}/F_{iO_2}. The second session of CHF reversed these changes (*Table 1*). The urinary flow, mean arterial blood pressure, systemic vascular resistance index and P_{aO_2}/F_{iO_2} from these four patients correlated inversely with plasma IL-6 or IL-8. For example, the correlation coefficient (r) value was 0·64 or 0·70 between systemic vascular resistance index and IL-6 or IL-8 ($n = 16$, $P < 0·01$; least square analysis). Three patients survived for 28 days.

Table 1 Changes in physiological and biochemical parameters and in plasma levels of cytokines in relation to treatment with continuous haemofiltration in a patient with sepsis following liver injury

	Time (h)			
	CHF		CHF	
	0	24	48	72
Pulse rate (per min)	134	125	150	123
Body temperature (°C)	36·7	37·9	39·7	37·6
Mean arterial blood pressure (mmHg)	90	90	64	80
Systemic vascular resistance index (kPa s per l per m²)	78·9	109·1	64·0	80·8
Left ventricular stroke work index (g m/m²)	49·7	42·7	25·0	50·9
P_{aO_2}/F_{iO_2} (kPa)	23·7	34·8	28 5	32·9
Oxygen extraction ratio (%)	0·24	0·35	0·29	0·33
Urinary flow rate (ml/h)	0 8	45·2	29 6	25·6
Creatinine (μmol/l)	424	380	380	301
TNF-α (pg/ml)	32·1	5·2	17 0	3·3
IL-1β (pg/ml)	<15·6	<15·6	<15·6	<15·6
IL-6 (pg/ml)	3340·0	254·0	443 0	47 6
IL-8 (pg/ml)	138·0	79·5	113·0	38 1

CHF, continuous haemofiltration; P_{aO_2}/F_{iO_2}, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, TNF, tumour necrosis factor; IL, interleukin

Discussion

The rebound rise of plasma IL-6 and IL-8 observed in four patients in the control period might imply that removal of cytokines by CHF exceeded the rate of natural decline of circulating cytokines and/or that the stimuli to produce cytokines persisted despite conventional therapy. The inverse correlation between cytokine levels and clinical parameters indicates that removal of cytokines by haemofiltration had beneficial effects on renal function, haemodynamics and oxygenation in the four patients. Although the validity of unselective removal of both favourable and undefined unfavourable substances by CHF still remains to be clarified, this procedure should be considered as an additional treatment to conventional therapy in patients with SIRS or MODS.

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Short note

Value of a weekly surgical x-ray meeting

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Surgical x-ray meetings attended by surgeons and radiologists are used for the clarification of x-ray reports and education of those present. Although the value of these meetings is generally accepted in terms of education, it is not known in what way they contribute to patient management. An audit of the authors' weekly surgical x-ray meeting to determine whether such reports and management decisions are modified following review and whether this is of benefit to patients is described.

Patients and methods

Audit of the weekly surgical x-ray meeting for one team of three consultant surgeons was carried out during a period of 10 months. Thirty-six meetings took place, eight were cancelled because of holidays or other meetings. Data were collected prospectively by one surgeon (R.M.C.) during 30 meetings but no data were recorded when he was absent (six occasions). The x-rays of 225 patients (median number of patients per meeting 7, range 2–17), 219 (97 per cent) of whom were being investigated for disorders of the gastrointestinal tract, were presented by members of the surgical team and reviewed by one of two consultant radiologists with an interest in gastrointestinal disease. A previous report had already been issued in 172 patients (76 per cent) and this original report and the management decision before review were recorded for each patient. Following a further report issued at the review meeting, the original management decision was either confirmed or modified. At least 12 months after the meeting the records of those patients in whom review led to a clinical decision being modified were audited.

Results

Of the 172 patients with a previous x-ray report, 30 (17 per cent) had a final report that differed. In one patient the review radiologist altered his own report, while in 29 a colleague's report was revised. Following review and further discussion the management decision before review was altered in 50 patients (29 per cent); this was based exclusively on the revised x-ray report in 22 (13 per cent) (*Table 1*). The four cancelled operations were perineal sinus exploration, submandibular duct exploration, cholecystectomy and right hemicolectomy. Subsequent note review in 15 patients showed that a different decision following review made no difference to long-term outcome (for example, ordering an additional test failed to yield anything). Outcome following a change in decision was beneficial in five patients. Previously planned surgery (exploration of submandibular duct and right hemicolectomy) was justifiably cancelled in two patients. A colonoscopy recommended in one patient following x-ray review was carried out and a tubulovillous adenoma was identified and removed. Additional imaging investigations in two patients identified a carcinoma of the ovary and symptomatic jejunal diverticula.

Table 1 Changes in patient management following alterations in the x-ray report

	No. of patients
Cancellation of:	
Operation	4
Contrast radiography	3
Colonoscopy	3
Flexible sigmoidoscopy	2
Modification of:	
Endoscopic procedure to other endoscopic procedure	2
Endoscopic procedure to contrast radiography	2
Initiation of:	
Further laboratory tests	2
Imaging procedure (ultrasonography)	2
Endoscopic procedure	2

A decision was made to cancel a previously arranged colonoscopy in one patient because it was wrongly thought that the barium enema had excluded malignant disease. This resulted in a rectosigmoid carcinoma remaining undiagnosed for a further 14 months.

Discussion

Review of radiographs is encouraged in breast screening[1,2], but its value in changing patient management in other fields has not previously been demonstrated. By identifying the management decision before review, the authors have shown that review of the x-rays and subsequent discussion resulted in an alteration in management in 29 per cent of patients: this was found to be directly as a result of the review in 13 per cent. Apart from the educational benefit of the meeting, x-ray review is of value in refining decision making in patients with

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gastrointestinal disease. This refinement usually did not affect final outcome, but five patients benefited. Unfortunately, the review also delayed the diagnosis of a rectosigmoid carcinoma.

A weekly x-ray meeting is a valuable medium in which to review x-rays and discuss changes in patient management. Such review results in the alteration of a significant number of reports which may contribute to changes in management.

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Correlation between Acute Physiology and Chronic Health Evaluation (APACHE) III score and immunological parameters in critically ill patients with sepsis

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A relationship between physiological parameters of severe sepsis and immunological function has not been established. In ten severely ill patients with sepsis physiological risk was assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) III score, while one component of immunological function was evaluated using peripheral blood mononuclear cell (PBMC) cytokine production after stimulation with lipopolysaccharide (LPS) *in vitro*. Five of the ten patients died. Mean(s.e.m.) APACHE III scores at admission were not significantly different between survivors and non-survivors (82(13) *versus* 95(13)) but after 72 h they were lower in survivors (51(13) *versus* 111(15), $P < 0.05$). Downregulation of cytokine production by PBMC on LPS stimulation was a transient event in survivors. Survivors had a three-fold increase in tumour necrosis factor α bioactivity within 72 h, but there was no increase in non-survivors. A similar pattern was demonstrated for interleukin (IL) 1β ($P < 0.05$ between survivors and non-survivors) and IL-6 ($P = 0.06$) immunoactivity. Physiological as well as immunological parameters in critically ill patients with sepsis independently predicted hospital survival ($r^2 = 0.2$). These data demonstrate a relationship between the pattern of cytokine production *in vitro* and survival.

Clinical assessment of patients in a surgical intensive care unit (ICU) relies on methods that discriminate between severity of illness and clinical outcome. Research has focused on quantifying disease severity as well as estimating prognosis and outcome[1–4]. Several indices have been developed which predict mortality of adult patients admitted to ICUs[5–7]. The Acute Physiology and Chronic Health Evaluation (APACHE) II score developed by Knaus *et al.*[8] is the most widely tested and validated[9–11].

Recently, Knaus *et al.*[12] presented a revised and improved form of APACHE II, termed the APACHE III prognostic system. This system may reduce uncertainty about difficult clinical decisions and may be used by physicians to direct health care towards more scientific and ethical approaches[13]. The new prognostic system has two components, the APACHE III score and the APACHE III predictive equation. The latter uses the APACHE III score and reference data on major disease categories and treatment location immediately before admission to the ICU.

Physiological parameters included in the APACHE III score are, at least in part, regulated by the production of proinflammatory cytokines. Some studies have demonstrated a correlation between outcome and raised cytokine levels in the circulation[14–18]. Research has also focused on *in vitro* cytokine production by cells or cell systems as prediction modalities[19–25]. The ability of peripheral blood mononuclear cells (PBMC) to produce cytokines following stimulation with lipopolysaccharide (LPS) has been investigated most commonly.

In the present study mononuclear cell function in patients with sepsis in the surgical ICU was investigated. *In vitro* cytokine production by PBMC was evaluated over 72 h following admission to the ICU and was compared with the objective probability estimates of the APACHE III score.

Patients and methods

Ten critically ill patients (six men, four women) were included in the study. These patients were all admitted to the surgical ICU with septic shock as defined by criteria published previously[26]. A positive culture from an otherwise sterile site was also required. Ventilatory support, appropriate fluid resuscitation and haemodynamic support was needed by all patients for more than 2 days. Other evidence of organ dysfunction included a creatinine level of more than 2·0 mg/dl ($n = 8$) and total bilirubin concentration above 2·0 mg/dl ($n = 6$). The patients' clinical status was evaluated at the time of initial blood sampling and after 72 h using the APACHE III score. A positive culture for Gram-negative bacterial sepsis was obtained from blood, sputum, or urine in all patients. All patients received antibiotics believed appropriate for their clinical source of infection; specific measures for selective gut decontamination were not used. Six patients entered the ICU after operation. Patient demographics and diagnosis are listed in *Table 1*.

Mononuclear cell function and cytokine response were evaluated at 24-h intervals over the first 72 h in the ICU. PBMC were isolated using a modification of published methods[27]. Anticoagulated blood (treated with ethylenediamine tetra-acetic acid) was diluted with an equal volume of RPMI 1640 culture medium containing gentamicin 50 μg/ml. A 10-ml aliquot of diluted blood was layered over 4 ml Histopaque 1.077 (Sigma Diagnostics, St Louis, Missouri, USA) and centrifuged for 35 min at 1500*g* at room temperature. The interface containing mononuclear cells was removed, washed with RPMI 1640 and pelleted by centrifugation at 1500*g* for 8 min. Cells were reconstituted in complete medium (RPMI 1640 containing 10 per cent heat-inactivated fetal calf serum) at a final concentration of 10^6 cells/ml and plated into 24-well microtitre plates at 37°C in 5 per cent carbon dioxide. After 90 min, non-adherent cells were removed by gently washing the plates twice with complete medium. The adherent mononuclear cells were then stimulated with 1 μg LPS (concentration 1 μg/ml, from

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Table 1 Demographics of ten critically ill patients in the intensive care unit with septic shock syndrome

Patient no.	Sex	Age (years)	Diagnosis in intensive care	Micro-organism	Source	LAL activity (ng/ml)	Outcome at day 28
1	M	57	AAA, peritonitis	*Escherichia coli*	Peritoneal fluid	6·25	Died on day 28
2	F	80	Colonic resection	*Enterobacter cloacae*	Bile fluid	3·09	Died on day 14
3	M	80	AAA, pneumonia	*Proteus mirabilis*	Lung	1·63	Died on day 21
4	F	27	Subfascial abscess	*Enterobacter faecalis*	Blood	0·41	Alive
5	M	58	Pneumonia	*Escherichia coli*	Lung	1·28	Alive
6	F	74	Intra-abdominal abscess	*Citrobacter* sp.	Blood	3·10	Alive
7	M	67	Acute pancreatitis	Mixed culture	Blood	0·79	Alive
8	M	78	Sepsis, MOF	Mixed culture	Lung	0·18	Died on day 1
9	M	71	Sepsis, MOF	Mixed culture	Blood	0·48	Died on day 4
10	F	66	Pelvic abscess	*Escherichia coli*	Blood	1·14	Alive

AAA, abdominal aortic aneurysm; MOF, multiple organ failure, LAL, limulus amoebocyte lysate (endotoxin assay)

Escherichia coli serotype 0127 : B8 (Sigma, Lot 69F4001)) Control cells did not receive endotoxin Cells were incubated for 18 h and cell supernatants harvested and stored at −70°C for future assay of cytokines, tumour necrosis factor (TNF)α, interleukin (IL) 6 and IL-1β

Concurrent with collection of PBMC from arterial blood, plasma TNF-α, IL-1β and endotoxin activity were also measured.

Endotoxin levels were determined using an endotoxin-specific chromogenic limulus test (Endospecy test; Seikagaku Corporation, Tokyo, Japan). The sensitivity of this method was 2 pg/ml and the coefficient of variation of the assay was 8 per cent TNF-α cytotoxicity was assessed using the WEHI 164 clone 13 fibroblast bioassay[28], which had a sensitivity of 15–30 pg/ml. IL-1β and IL-6 were determined by enzyme-linked immunosorbent assay (ELISA) as described previously[14]. The sandwich ELISA uses two monoclonal antibodies, one biotinylated, and signal amplification is achieved through a biotin–streptavidin-conjugated horseradish peroxidase system. The sensitivity of the assay was 10 pg/ml for IL-1β and 35 pg/ml for IL-6.

The APACHE III score was applied as described elsewhere[12] The scoring points for the categories physiology, admission, diagnosis and surgical status range between zero and 252, for chronic health between zero and 23, and for age between zero and 24 (total range 0–299).

The study was approved by the Institutional Review Board of the New York Hospital–Cornell Medical Centre and informed written consent was obtained from the patient or a responsible family member before entry into the study.

Statistical analysis

Values are presented as mean(s.e.m.). *In vitro* cytokine production was compared between time zero and 72 h, and between survivors and non-survivors, by Student's *t* test. Correlation between APACHE III score and *in vitro* cytokine production was performed using linear regression and least squares analysis. All statistical analyses were performed on a Macintosh-based personal computer system employing the JMP biostatistical package (SAS Institute, Cary, North Carolina, USA). Significance was designated at the 95 per cent confidence interval using a two-tailed test.

Results

The APACHE III scores of both survivors and non-survivors at admission and after 72 h are shown in *Fig. 1*. One patient (no. 8) died within 48 h, while all others survived for at least 72 h (*Table 1*) at which point surviving patients had significantly ($P<0{\cdot}05$) lower APACHE III scores than non-survivors. In total, five patients died in the ICU; the remainder were discharged back to a surgical ward.

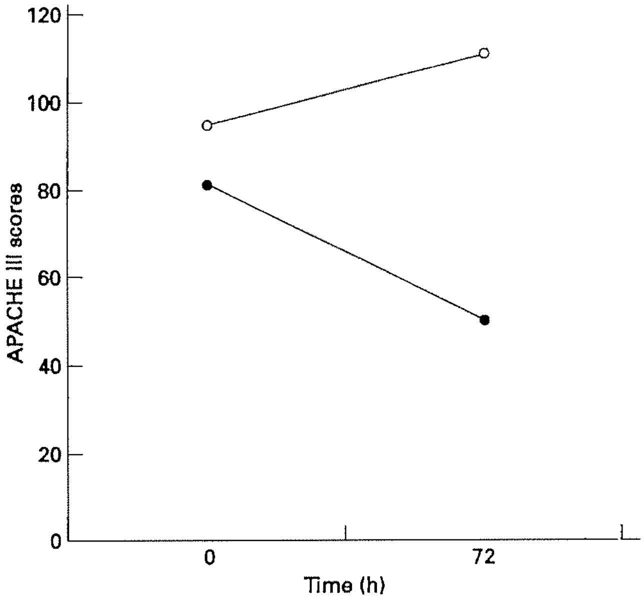

Fig. 1 Changes in Acute Physiology and Chronic Health Evaluation (APACHE) III score after 72 h in patients with sepsis. Scores were evaluated on admission to the intensive care unit and after 72 h APACHE III scores declined in survivors (●) and rose in patients who died (○). $P<0{\cdot}05$, Student's *t* test

Evaluation of the cytokine response of PBMC to LPS stimulation *in vitro* was performed daily over the first 72 h in nine patients; one patient died within 48 h (*Table 2*). Proinflammatory cytokines TNF-α, IL-1β and IL-6 were measured and data from survivors and non-survivors were compared. Survivors alone had increased TNF-α, IL-1β and IL-6 ($P=0{\cdot}06$) activity *in vitro*. *In vitro* cytokine profiles did not correlate with APACHE III scores ($r^2=0{\cdot}2$). Two patients (nos 7 and 9) had detectable plasma TNF activity at 72 h (207 pg/ml and 257 pg/ml respectively). Only patient 8 had detectable plasma IL-1β immunoactivity (54 pg/ml) at 72 h.

Endotoxin limulus amoebocyte lysate activity was detected in the plasma of all patients at study entry (range 0·18–6·25 ng/ml): survivors had a mean level of 1·34 ng/ml and non-survivors 2·33 ng/ml (*Table 1*). There was no

Table 2 Proinflammatory cytokine production *in vitro* by peripheral blood mononuclear cells from critically ill intensive care patients with sepsis following stimulation with lipopolysaccharide

	TNF-α		IL-1β		IL-6	
Time (h)	Survivors	Non-survivors	Survivors	Non-survivors	Survivors	Non-survivors
0 (Admission)	729(427)	1132(451)	281(167)	1505(346)	1194(385)	7804(3724)
24	1611(557)	2400(1398)	980(738)	1503(805)	3442(2643)	2195(877)
48	949(340)	1314(664)	398(232)	2535(2033)	3314(1838)	1138(666)
72	1991(789)	1058(584)	603(158)*	721(428)*	5478(2676)	996(361)

Values are mean(s.e.m.) pg per 10^6 peripheral blood mononuclear cells. TNF, tumour necrosis factor; IL, interleukin. $^*P<0.05$ *versus* admission value (Student's t test)

correlation between initial endotoxin level and duration of sepsis, survival or initial APACHE III score.

Discussion

Efforts to measure the severity of illness in patients in intensive care have spawned several different quantitative approaches[29,30]. In this study, the APACHE III prognostic system, which uses physiological indices, was evaluated. In addition, the patients' immunological response was assessed using cytokine production *in vitro* of freshly isolated PBMC. The latter investigation was selected because of a report by Munoz *et al.*[19], in which it was demonstrated that PBMC from patients with Gram-negative infections displayed a reduced LPS-induced production of cytokines *in vitro*. This downregulation of *in vitro* cytokine production presumably represents a transient refractoriness of monocytes following *in vivo* stimulation[31–34]. The phenomenon, referred to as endotoxin 'tolerance', in part reflects a reduced capacity to synthesize cytokines on re-exposure to endotoxin. Besides dysregulation at the transcriptional or post-transcriptional level[35,36], an alteration in recruitment from macrophage precursor pools is a possible underlying mechanism[37]. The hyporesponsive state of monocytes may also be an autocrine response to cytokine activity. TNF binding to monocytes results in both shedding of the extracellular domain of receptors[38], as well as internalization of ligand–receptor complexes[39], thereby resulting in a temporary hyporesponsiveness by mononuclear cells.

In the present study, PBMC from survivors displayed a recovery of *in vitro* cytokine production over 72 h, whereas those of non-survivors failed to demonstrate this response. Previous data from human volunteers[23] showed that 3 h after LPS administration *in vivo*, cytokine production by PBMC was suppressed to a mean(s.e.m.) of 64(6) per cent following subsequent *in vitro* LPS stimulation. This suppression was a transient event and was not observed 24 h later. Furthermore, the authors demonstrated that such suppression of cytokine production was not specific for endotoxin stimulation as both IL-1β and exotoxic shock toxin induced the same effect. Data from normal subjects studied also confirmed that the magnitude of cytokine production *in vitro* after LPS stimulation differs significantly between individuals (S. F. Lowry, unpublished results). Based on responses observed in normal subjects, it was the TNF responsive element that was largely inhibited initially in both groups of critically ill patients in the present study: mean TNF-α per 10^6 stimulated PBMC was 729 pg in survivors and 1132 pg in non-survivors *versus* 10 300 pg in healthy volunteers (unpublished data). In contrast, surviving patients had lower IL-1 and IL-6 levels than non-survivors at the outset. This is consistent with previous observations in some critically ill patients[40].

The present study demonstrated that recovery of critically ill patients with sepsis occurred concurrently with restoration of LPS-stimulated cytokine production by PBMC *in vitro*. This finding agrees with the report by Hershman *et al*[41], who demonstrated that human leucocyte antigen (HLA-DR) expression of PBMC following incubation with LPS distinguished survivors from those who died. The ability of PBMC to express HLA-DR correlated directly with the patients' clinical course and these measurements identified a group of patients at high risk of infection and death following trauma. These data also confirm the observations of Munoz *et al*[19,21], who demonstrated recovery of PBMC later in the recuperation process.

If recovery is dependent upon PBMC function, immunomodulatory intervention may be helpful in these patients. Faist *et al.*[42] reported that depression of cellular immunity after major injury correlates with the subsequent development of infection. In a subsequent study[43], the same authors concluded that negative regulatory macrophage function after severe injury may be the initial point of post-traumatic immune suppression, and suggested that if immunomodulatory therapy was to be successful, it should be aimed primarily at the restoration of the accessory cell–T cell interaction.

The APACHE III scores in the present patients were significantly lower 72 h after admission in survivors compared with non-survivors. On admission, mean APACHE III scores were similar. The finding that both physiological and immunological function in critically ill patients with sepsis demonstrated predictive value for hospital survival supports the strategy of physiological as well as immunological evaluation in these patients. There was no statistically significant correlation between physiological and immunological parameters.

While prediction of mortality using physiologically based scoring systems is well documented[40], these results show that immunological function, as evaluated by the *in vitro* cytokine production of PBMC, provides another means of prediction of outcome. Further studies with more patients are necessary to elucidate the interaction between clinical and immunological parameters. Efforts should be directed towards developing rapid immunological assays which may serve as adjunctive or independent methods of assessing mortality risk in patients with sepsis.

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Case report

Thoracoscopic implantation of an epicardial pacemaker

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The implantation of a pacemaker for the management of auriculoventricular block (AVB) is traditionally performed by inserting the electrocatheter into a peripheral vein and positioning the generator subcutaneously. In certain situations this is impossible and requires a subxiphoid approach or thoracotomy to implant an epicardial electrocatheter. This communication reports the thoracoscopic implantation of an epicardial pacemaker in a patient with AVB in whom insertion in the peripheral vein was impossible.

Case report

A 55-year-old woman was diagnosed with chronic renal insufficiency and included in a haemodialysis programme. The patient's clinical symptoms included nausea, vomiting and bradycardia of 47 beats per min; the AVB electrocardiogram revealed a heart rate of 45 beats per min with a nodal rhythm. Telemetry showed intercalated spells of complete auriculoventricular block at 45 beats per min and periods with a sinus rhythm at 70 beats per min. Echocardiography revealed concentric hypertrophy of the left ventricle, with preserved systolic function and signs of slight diastolic dysfunction.

Diagnosing high-grade AVB, it was decided to implant a pacemaker. The patient had a right arteriovenous fistula, for which reason implantation of the electrode was attempted through the left cephalic and jugular veins. The electrocatheter could not be inserted because of previous thrombosis of the innominate venous trunk. Implantation of the epicardial electrode using a thoracoscopic approach was therefore selected

Three trocars were inserted· one of diameter 10 mm in the sixth intercostal space at the mid-axillary line for placement of a straight telescope, and two of 5 mm in the fourth and seventh intercostal spaces at the anterior axillary line for placement of a croche and grasper. A 4-cm pericardial window was created anterior to the left phrenic nerve, and the electrocatheter was inserted through a counter-incision in the seventh intercostal space at the left parasternal line and screwed into the muscular mass of the myocardium, proximal to the cardiac apex. The electrocatheter was drawn out subcutaneously to the left hypochrondrium and connected to the generator (Biotronik Pikos LP-01, Berlin, Germany), which was implanted under the fascia of the greater oblique. A pleural aspiration drain was left, which was removed 48 h later after pulmonary re-expansion under radiological guidance. Following radiology and electrocardiography to test that the pacemaker was working correctly, the patient was confirmed to be asymptomatic and discharged 72 h after operation.

Discussion

In recent years, thoracoscopy has enabled a less aggressive access to the thoracic cavity and reduced the requirement for postoperative analgesia[1]. Clinical experience has increased, progressing from the creation of a therapeutic pneumothorax and adhesion lysis (as performed by Jacobaeus at the turn of the century[2]) to the present-day possibility of performing pulmonary resection, decortication, pericardiectomy, etc.

Thoracoscopy has been used recently to implant a cardioverter for the management of arrhythmia, using an opening in either the pericardium[3] or extrapericardium[4]. The subxiphoid laparoscopic approach has also been used to implant epicardial electrodes[5]. In the present case, the thoracoscopic approach was used to make a small pericardial incision instead of the large window created by others[3]. The electrode placement was done simply by screwing it into the myocardium. This technique proved a good alternative to the percutaneous vascular approach, which was impossible in this patient.

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Antioxidant depletion during aortic aneurysm repair

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Ischaemia–reperfusion injury generates oxygen-derived free radicals leading to local and distant damage. A simple method of following oxidative activity is to measure the consumption of endogenous scavenging antioxidants; an enhanced chemiluminescent assay was used to study this phenomenon in 21 patients undergoing surgery for abdominal aortic aneurysm (AAA). Samples of peripheral venous blood were taken before induction of anaesthesia and then from a central venous line and the inferior mesenteric vein before, during, and after clamping of the aorta. Further specimens were taken from the central line at 2, 6 and 24 h after operation. Antioxidant concentration in the peripheral, central and inferior mesenteric blood were similar, indicating that anaesthesia and surgical dissection had no effect. Levels decreased significantly in central and inferior mesenteric blood during and after clamping, but returned to normal by 24 h. These results confirm ischaemia–reperfusion phenomena in AAA repair.

Severe skeletal muscle ischaemia followed by reperfusion with oxygenated blood leads to potentially lethal complications, including pulmonary oedema[1] and renal failure[2]. It has been proposed that metabolism of oxygen, after a period of ischaemia, resulting in the generation of toxic free radical species plays an important role in the pathophysiology of this reperfusion injury[3]. Oxidative damage has also been implicated in several other disease processes, including rheumatoid arthritis[4], diabetes mellitus[5], atherosclerosis, carcinogenesis and the effects of ionizing radiation[6,7]. Ischaemia of the lower torso during infrarenal abdominal aortic aneurysm (AAA) repair has been shown to initiate systemic changes after reperfusion which result in increased albumin excretion by the kidneys, manifested as microalbuminuria[8]. This is considered to indicate a generalized increase in endothelial permeability secondary to damage or dysfunction.

Because of their high reactivity and consequent short half-lives, direct measurement of free radical production has proved difficult[9]. Most studies have relied on indirect evidence from the generation of reaction products, such as conjugated dienes[9], or the impact of free radical scavenging therapy. Recently, electron spin resonance spectroscopy has provided direct evidence of free radical production in an animal model of renal ischaemia and reperfusion[10].

Antioxidants provide the first line of defence against oxygen-derived free radicals. Consumption of endogenous scavenging antioxidants provides a simple method of following oxidative activity. Studies have concentrated on individual antioxidants such as ascorbate[11] and α-tocopherol[12]. However, because the relative importance of individual antioxidants varies with different situations, a variety of newer techniques have been developed to measure total free radical scavenging (antioxidant) activity in biological fluids[13]. In the present study an enhanced chemiluminescent (ECL) assay for total plasma antioxidant activity in patients undergoing AAA surgery was performed. The assay is based on the enzyme horseradish peroxidase (HRP) catalysing the reaction between a hydrogen donor, such as the chemiluminescent substrate luminol, and a hydrogen acceptor (oxidant), such as perborate. Light emission in this system becomes constant by the addition of an enhancer such as *para*-iodophenol[14] and depends on the constant production of free radical intermediates derived from *para*-iodophenol, luminol and oxygen. The light emission is, therefore, sensitive to interference by radical scavenging antioxidants and the duration of suppression is proportional to the concentration of antioxidants[15].

Patients and methods

Approval for this study was obtained from the local research ethics committee. Twenty-one patients undergoing elective infrarenal AAA surgery were studied (19 men and two women) of mean age 70 (range 63–82) years. Patients with a history of major respiratory or renal disease were excluded, as were those receiving non-steroidal anti-inflammatory drugs. All patients had central venous pressure lines and Swan–Ganz catheters to ensure constant blood volume and optimum stable cardiac performance throughout the procedure. Mean aortic clamp time was 59 (range 45–78) min.

Blood samples were taken from an antecubital vein before the induction of anaesthesia, and then from both a central venous line and the inferior mesenteric vein (cannulated during the initial dissection) before clamping the infrarenal aorta, on completion of the proximal anastomosis (i.e. during aortic clamping), and 5 min after the release of the clamp. Further specimens were taken from the central venous line at 2, 6 and 24 h after operation. The blood was collected in sterile bottles with ethylene diamine tetra-acetic acid as anticoagulant and immediately centrifuged at 2000*g* for 10 min. The plasma was snap-frozen in liquid nitrogen and stored at −70°C for subsequent antioxidant analysis. Urine was collected before operation and every hour after induction of general anaesthesia. The urine was also snap-frozen for subsequent analysis of albumin concentration.

ECL immunoassay signal reagent and HRP–conjugate (mouse immunoglobulin G HRP-linked whole antibody from sheep) were obtained from Kodak Clinical Diagnostics (Amersham, UK). Signal reagent consists of assay buffer to which tablets A and B are added containing luminol, enhancer and oxidant. Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid),

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a water-soluble α-tocopherol analogue, was obtained from Aldrich (Dorset, UK). A luminometer based on a side-window photomultiplier tube (EMI/type 9781A, 94 μAmp/lumen; Thorn EMI, Middlesex, UK) was used to measure chemiluminescent emission.

The ECL assay procedure has been described previously[15]. The time in seconds from the point of suppression of light emission until a 10 per cent recovery was measured and compared with values for standard Trolox solution. The total antioxidant activity was then expressed in μmol/l. The ECL assay has a coefficient of variation of 5·0 per cent between batches and 2·0 per cent within batches ($n = 60$).

Urinary albumin content was determined using a double-antibody ^{125}I-radioimmunoassay (Diagnostic Products, Wallingford, UK). The result was expressed as an albumin:creatinine ratio (ACR) in mg/mmol to compensate for changes in urinary flow during the investigation.

Antioxidant levels from different sources (i.e. peripheral, central venous and inferior mesenteric vein blood) were compared using the Mann–Whitney *U* test. Levels from the same source at different time points were compared with the Wilcoxon signed rank test. The results were considered significant at $P < 0·05$.

Results

Changes in renal albumin excretion are shown in *Fig. 1*. There were statistically significant percentage increases in the ACR from 1 to 7 h after induction of general anaesthesia, compared with levels before operation, and again from 14 to 24 h ($P < 0·05$, Wilcoxon signed rank test).

Changes in total plasma antioxidant activity are shown in *Fig. 2*. There were no statistically significant differences between the levels in peripheral plasma before operation, central venous plasma before aortic clamping and inferior mesenteric plasma before aortic clamping. Antioxidant levels in central venous blood decreased significantly during aortic clamping ($P < 0·0001$) and on release of clamping ($P < 0·0001$) compared with levels before clamping. Levels returned to preoperative values by 24 h after surgery ($P = 0·14$). Antioxidant levels in inferior mesenteric vein blood also decreased significantly during aortic clamping ($P < 0·01$) and on release of clamping ($P < 0·0001$), compared with levels before clamp application.

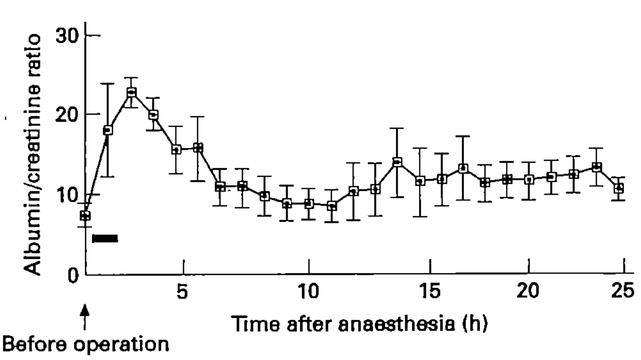

Fig. 1 Changes in renal albumin excretion (expressed as albumin: creatinine ratio) over the 24-h period after induction of general anaesthesia. Values are means and the error bars represent s.e.m. There are statistically significant percentage increases for the first 7 h and from 14 to 24-h ($P < 0·05$, Wilcoxon signed rank test). The shaded area represents the duration of aortic clamping

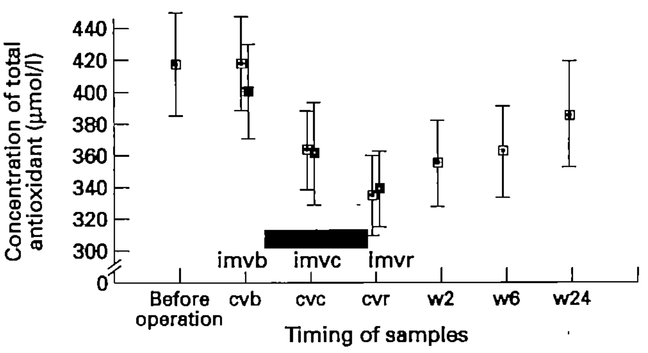

Fig. 2 Total antioxidant levels for 21 patients undergoing aortic surgery expressed as μmol trolox equivalent per litre. Values are given as mean and error bars represent s.e.m. Before operation, peripheral preoperative venous blood; cvb, cvc, cvr central venous blood before, during and after aortic clamping respectively (□); imvb, imvc, imvr, inferior mesenteric vein blood before, during and after aortic clamping (■); w2, w6, w24, central venous blood 2, 6 and 24 h after operation. The shaded area represents the duration of aortic clamping

Eight of the 21 patients developed complications: stroke (one), atrial fibrillation (one), chest infections (two), shortness of breath due to pulmonary oedema (two) and peripheral emboli requiring embolectomy (two). Seven of the 21 patients were current smokers. There were no associations between antioxidant levels and smoking or the development of complications.

Discussion

It has been suggested that aortic clamping and reperfusion initiate a systemic inflammatory response, producing endothelial damage and an increase in vascular permeability[8]. In the lungs this is manifested by non-cardiogenic pulmonary oedema[1] and in the kidneys by increased urinary protein excretion (microalbuminuria)[8]. This manifestation of microalbuminuria was noted in the present study. Microalbuminuria has been demonstrated after a variety of injuries[16,17] and can be considered to reflect vascular endothelial injury.

A central biochemical feature of ischaemia–reperfusion is the generation of oxygen-derived free radicals[3]. Direct measurement of free radicals is difficult because of their high reactivity and short lives. Endogenous antioxidants provide the first-line defence against these oxidants and, therefore, a decrease in total antioxidant activity would be expected with reperfusion. This has been shown previously, in patients undergoing aortic surgery, by measuring α-tocopherol (vitamin E)[12] alone. However, several antioxidants are involved and all have different relative importances[13]. Individual antioxidants and co-factors are affected by dietary intake[18], whereas total antioxidant activity may be less affected. Therefore, total antioxidant activity was measured.

The changes seen are unlikely to be caused by surgical trauma as there is no difference between antioxidant levels before operation and before clamping the aorta. Several possible reasons for the changes, apart from ischaemia–reperfusion, must be considered. Transport and uptake phenomena may contribute to these changes. Loss of circulating volume replaced by antioxidant-free colloids may be the explanation, but this does not explain the steady rise in antioxidant levels after the operation to preoperative levels by 24 h. Haemodilution secondary to deliberate fluid overload in preparation for removal of the aortic clamp is a possible explanation, but this has not been supported by previous studies[12].

Therefore, the changes in total antioxidant activity in patients undergoing aortic surgery indicate the generation of free radicals. There was no correlation, however, with antioxidant levels in individual patients and the risk of postoperative complications. This is not surprising, as free-radical generation is the first step in a complex cascade of events, involving neutrophils and many soluble mediators[19], and so many other factors would need to be taken into account before such correlations could be considered likely.

Of interest was the marked decrease in antioxidant levels during clamping, before the expected generation of free radicals on reperfusion. This has been noted previously[12,20], and is caused by partial ischaemia resulting from collateral blood supply to the lower torso and gastrointestinal organs during aortic clamping. Murphy *et al.*[12] have shown that antioxidant consumption occurs during aortic clamping whereas lipid peroxidation (the result of free-radical damage) is more marked during reperfusion. Rao and Mueller[21] have suggested that, even during severe ischaemia, the oxygen tension is sufficient to support free-radical reactions. This has implications for the timing of any adjuvant antioxidant treatment that may be considered in these patients, as the period of ischaemia as well as the period of reperfusion may be important in terms of the outcome.

The results suggest that the absolute levels and decreases in antioxidant levels are similar for systemic and gut circulations, despite the differences in tissue volume. However, there is close correlation (correlation coefficient $>0{\cdot}93$ for all three sampling time points) between antioxidant levels from central and inferior mesenteric venous blood, suggesting that the gut changes are merely a reflection of systemic changes.

In conclusion, a change in total antioxidant activity which supports the concept of ischaemia–reperfusion dysfunction in patients undergoing AAA surgery has been demonstrated. The importance of the time at which changes in antioxidant levels occur with respect to potential therapeutic options needs further study.

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Diagnosis of arterial disease of the lower extremities with duplex ultrasonography

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The development of duplex scanning carries the prospect of an entire non-invasive work-up of patients with peripheral arterial occlusive disease. To obtain the best available estimates of its diagnostic accuracy, a meta-analysis of 71 studies evaluating duplex scanning was performed. Independent methodological judgement left 16 studies for data extraction. Pooled estimates (95 per cent confidence interval of sensitivity and specificity for detection of a stenosis greater than or equal to 50 per cent or occlusion in the aortoiliac tract were 86 (80–91) per cent and 97 (95–99) per cent respectively. The results for the femoropopliteal tract compared well with this, with a sensitivity of 80 (74–85) per cent and a specificity of 96 (94–98) per cent. The accuracy of detection of a stenosis greater than or equal to 50 per cent or an occlusion in the infragenicular arteries was lower with a sensitivity and specificity of 83 (59–96) per cent and 84 (69–93) per cent respectively. Duplex scanning is an accurate tool for assessment of atherosclerotic lesions in the aortoiliac and femoropopliteal tract and can replace routine pre-interventional angiography in a substantial number of patients.

Duplex scanning is a relatively new diagnostic modality in vascular disease that facilitates non-invasive acquisition of anatomical and physiological information. Changes in a cross-sectional area of the vascular lumen can be determined by means of peak systolic velocity (PSV) at the site of a stenosis, the ratio of PSV at the site of the stenosis and its immediate normal vicinity, end diastolic velocity, and more subjective criteria such as number of phases in the Doppler waveform and degree of spectral broadening. This development carries the prospect of an entire non-invasive work-up of patients with peripheral arterial occlusive disease (PAOD).

Before a new test can be introduced to routine clinical practice and used as a base for clinical decisions it should be evaluated in methodologically sound studies. In order to obtain the best available estimates of the accuracy of this non-invasive tool a systemic literature review was performed and applied methodological criteria were used in the present analysis.

Materials and methods

Study selection

A MEDLINE search was performed between 1976 and June 1994 to retrieve all publications in English, German and Dutch on diagnostic tests in PAOD. The keywords used were arterial occlusive disease, arteriosclerosis, 'claudica*' and vascular disease under the conditions of human and lower extremity Exclusion criteria were child and adolescence, anaesthesia, neoplasm, wound and injury, and varicose veins. Based on title and abstract all publications on diagnostic tests were selected by one observer. Accuracy of selection was controlled in a random sample of 100 publications yielding interobserver kappas of 0·81, 0·85 and 0·91. Bibliographies from the selected articles were used to complete the search. Publications reporting repeatedly on the same study population were included only once

Qualitative analysis

All articles on duplex scanning were read by three independent observers and divided into three categories: pilot studies (e.g. case reports, reproducibility studies), formal analysis studies (comparing duplex with angiography as gold standard) and review articles. As, in most studies, angiography was the gold standard it was used as such in the present meta-analysis, without restrictions to angiographic technique or criteria for disease.

The same observers independently graded methodological quality of the gold standard studies according to predefined criteria. Two elements were essential: a clear definition of the study population and a clear description of the duplex scanning technique. Secondary criteria to improve study quality were a series of consecutive patients, a prospective study, predefined test criteria and independent assessment of duplex scanning and angiography. Studies satisfying all criteria were graded level 1, studies satisfying at least the two essential criteria level 2, and the remaining studies level 3. Discrepancies in judgement were discussed in order to arrive at a unanimous decision.

Quantitative analysis

Gold standard studies reporting sensitivity and specificity proceeded to quantitative analysis. Raw data were extracted by two observers to summarize diagnostic accuracy according to a modification of the method proposed by Midgette *et al.*[1] A test of homogeneity (Fisher's exact or χ^2 test) was initially applied to determine whether differences in sensitivity and specificity among studies of comparable methodological level were potentially a result of chance alone. When homogeneity could not be rejected, pooled estimates of sensitivity and specificity and 95 per cent confidence interval (c.i.) were calculated according to the DerSimonian and Laird[2] random effects model, to give maximum weight to potential sources of variation. In case of heterogeneity the Spearman correlation between the separate sensitivities and (100-specificities) was determined. Midgette *et al.*[1] proposed fitting of a summary receiver-operating curve to determine optimal test criteria in case of a positive correlation, a procedure described in detail by Littenberg and Moses[3].

Three different vascular segments were analysed: the aortoiliac tract extending from the infrarenal abdominal aorta to the common femoral artery; the femoropopliteal tract from the

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common femoral artery to the trifurcation; and the infragenicular arteries from the trifurcation to the pedal arteries. Some authors subdivided these segments into smaller parts but their reported diagnostic accuracy would be too optimistic because a false-negative or false-positive result was compensated for by the large number of accurate results. Moreover, when data of such studies are pooled, confidence intervals of the estimated sensitivity and specificity will be artificially narrow. In these studies, therefore, the results were transformed by dividing the raw data for the respective vascular segments by the number of subdivisions made to approximate the actual number of segments examined. If possible, accuracy for detection of a stenosis greater than or equal to 50 per cent, an occlusion, or both separately was determined because the findings will lead to different treatment strategies.

Results

Study selection and qualitative analysis

From a total of 6993 studies, 636 reported on the evaluation of diagnostic tests in PAOD, including 15 pilot studies, 16 review articles and 40 gold standard studies[4–43] on duplex ultrasonography*. None of the review articles provided original data and reviews were only used to complete the search. Six gold standard studies were excluded because they were double reports[4–9]. The remaining 34 studies are listed in *Table 1*. Six studies satisfied all methodological criteria[10–15], 15 met at least the two essential criteria[16–30], and 13 publications were of lower methodological quality[31–43].

Quantitative analysis

Four level 2 studies were excluded from quantitative analysis because of unspecified cut-off criteria[25], study population[26], unspecified investigated segment[27] or unclear angiographic criteria[29]. All level 3 studies were excluded because, owing to methodological shortcomings, no inference could be drawn from the results. Duplex scanning results extracted from the 16 remaining level 1

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*A complete reference list is available from the authors on request

Table 1 Results of qualitative analysis

Reference	Year	Criteria satisfied	Population	Scanning technique
Level 1				
Koennecke *et al.*[10]	1989	All	Chronic PAOD	Colour coded
Polak *et al.*[11]	1990	All	Claudication, critical ischaemia	Colour coded
Whelan *et al.*[12]	1992	All	Investigation of PAOD	Colour coded
Moneta *et al.*[13]	1992	All	Claudication, critical ischaemia	Colour coded
Hatsukami *et al.*[14]	1992	All	Severe claudication, critical ischaemia	Colour Doppler
Baxter and Polak[15]	1993	All	Claudication, critical ischaemia, cellulitis	Colour Doppler
Level 2				
Jager *et al.*[16]	1985	1, 3, 4, 5, 6	Claudication, rest pain, gangrene	B/W coded
Kohler *et al.*[17]	1987	1, 3, 4, 5, 6	Symptomatic PAOD	B/W coded
Langsfeld *et al.*[18]	1988	1, 4, 5	Claudication, critical ischaemia	B/W coded
Collier *et al.*[19]	1990	1, 2, 4, 5	Normal femoral, week/absent distal pulses	Colour Doppler
Legemate *et al.*[20]	1991	1, 3, 4, 5, 6	Claudication, critical ischaemia	B/W coded
Legemate *et al.*[21]	1991	1, 3, 4, 5, 6	Claudication, critical ischaemia	B/W coded
Whyman *et al.*[22]	1992	1, 3, 4, 5, 6	Calf claudication, referred for PTA	Colour Doppler
Davies *et al.*[23]	1992	1, 3, 4, 5	Claudication, referred for PTA	Colour coded
Vashist *et al.*[24]	1992	1, 3, 4, 5, 6	Claudication	Colour coded
Sacks *et al.*[25]	1992	1, 3, 4	Claudication, critical ischaemia	B/W coded
Fowkes *et al.*[26]	1992	1, 2, 4, 5, 6	Duplex for screening in general population	B/W coded
Ebner *et al.*[27]	1992	1, 4, 5	Claudication	Colour coded
Karasch *et al.*[28]	1993	1, 3, 4, 5, 6	Claudication, clinically suspected AOD	Colour coded
Langholz *et al.*[29]	1993	1, 4, 5, 6	Fontaine I–IV	Colour coded
Allard *et al.*[30]	1994	1, 3, 4, 5, 6	Claudication, rest pain, gangrene, other	B/W coded
Level 3				
Mergelsberg *et al.*[31]	1986	None	Suspicion of PAOD	B/W coded
Metz *et al.*[32]	1988	6	No clinical description of patients	B/W and colour coded
Hübsch *et al.*[33]	1988	4	Patients referred for duplex examination	Colour coded
Hendrickx *et al.*[34]	1989	6	No description	Colour coded
Seifert and Jager[35]	1989	4, 5, 6	No description	B/W coded
Cossman *et al.*[36]	1989	4, 5, 6	Patients referred for excimer laser angioplasty	Colour coded
Jager[37]	1989	None	No description	B/W coded?
Landwehr and Lackner[38]	1990	3, 4, 5	Patients referred for PTA	Colour coded
Mulligan *et al.*[39]	1991	3, 4, 5, 6	Symptomatic PAOD	Colour coded
Edwards *et al.*[40]	1991	1, 5	Ischaemic PAD	B/W coded
Baumgartner *et al.*[41]	1991	1, 3	Patients referred for PTA	B/W coded?
Ranke *et al.*[42]	1992	4, 6	Symptomatic PAOD	B/W coded
Van der Heijden *et al.*[43]	1993	1, 5	Patients referred for PTA	Colour coded

Criteria for methodological quality: 1, clear definition of study population; 2, consecutive patients; 3, prospective study; 4, clear description of duplex technique used; 5, predefined cut-off values; 6, independent assessment of duplex and angiography. PAOD, peripheral arterial occlusive disease; PTA, percutaneous transluminal angioplasty; AOD, arterial occlusive disease; PAD, peripheral arterial disease; B/W, black and white and 2 studies are listed in *Table 2*. Results for the different vascular segment are presented separately†.

Aortoiliac segment

Five studies[10,12,15,18,20] provided raw data on detection of a stenosis greater than or equal to 50 per cent. Three studies[10,12,15] were excluded because waveform and PSV ratios in the common femoral artery were interpreted to infer disease, without complete visualization of the iliac artery, and were therefore considered not to represent the entire aortoiliac tract. Of the two remaining studies[18,20] heterogeneity of sensitivity and specificity could not be detected ($P = 1{\cdot}0$ and $P = 1{\cdot}0$ respectively), resulting in a pooled sensitivity (95 per cent c.i.) of 80 (61–93) per cent and specificity of 95 (91–98) per cent (*Table 2*). The same studies[18,20] provided data on detection of an occlusion (*Table 2*). As there were no false-positive or false-negative results, homogeneity of sensitivity and specificity was assumed giving a pooled (95 per cent c.i.) sensitivity of 94 (65–100) per cent and specificity of 99 (98–100) per cent. Six studies[13,16,18,21,24,30] reported on detection of a diameter reduction greater than or equal to 50 per cent, occlusions included (*Table 2*). Data from level 1 and 2 studies were pooled because sensitivities and specificities were not heterogeneous among studies ($P = 0{\cdot}78$ and $P = 0{\cdot}13$ respectively) and did not seem to be influenced by methodological level. This led to pooled estimates (95 per cent c.i.) of 86 (80–91) per cent for sensitivity and 97 (95–99) per cent for specificity.

Femoropopliteal segment

For assessment of the femoropopliteal segment all authors applied the same criteria as for the aortoiliac tract. Four level 1[10–12,15] and two level 2[22,23] studies provided raw data on detection of a stenosis greater than

Table 2 Results of quantitative analysis for detection of a stenosis greater than or equal to 50 per cent, an occlusion and a stenosis greater than or equal to 50 per cent or occlusion

			Stenosis ≥ 50 per cent		Occlusion		Stenosis ≥ 50 per cent or occlusion	
Reference	Duplex criteria*	*n*	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Aortoiliac								
Level 1								
Moneta *et al.*[13]	PSV ratio > 2·0†	286	—	—	—	—	89	99
Level 2								
Jager *et al.*[16]	PSV ratio > 2·0	54	—	—	—	—	82	100
Langsfeld *et al.*[18]	PSV ratio > 2·0‡	46	80	95	100	100	86	94
Legemate *et al*[20]	PSV ratio > 2·5	90	81	96	88	100	—	—
Legemate *et al.*[21]	PSV ratio > 2·5	122¶	—	—	—	—	89	98
Vashist *et al*[24]	PSV ratio > 2·0	18	—	—	—	—	88	100
Allard *et al.*[30]	PSV ratio > 2·0	99	—	—	—	—	83	96
Pooled (95 per cent c.i.)			80 (61–93)	95 (91–98)	94 (65–100)	99 (98–100)	86 (80–91)	97 (95–99)
Femoropopliteal								
Level 1								
Koennecke *et al*[10]	PSV ratio > 2·0	82	71	96	87	96	95	100
Polak *et al.*[11]	PSV ratio > 2·0§	34	76	96	100	96	88	96
Whelan *et al*[12]	PSV ratio > 2·0**	100	88	96	95	99	—	—
Moneta *et al*[13]	PSV ratio > 2·0†	286	—	—	—	—	79	98
Hatsukami *et al.*[14]	Waveform††	58‡‡	—	—	90	97	70	96
Baxter *et al.*[15]	PSV ratio > 1·8	40	82	96	—	—	—	—
Pooled (95 per cent c.i.)			82 (67–92)	96 (93–98)	90 (80–96)	97 (94–99)	80 (70–87)	98 (95–99)
Level 2								
Jager *et al.*[16]	PSV ratio > 2·0	54	—	—	—	—	75	96
Legemate *et al*[21]	PSV ratio > 2·5	122¶	—	—	—	—	76	97
Whyman *et al.*[22]	PSV ratio > 2·0	36	93	96	100	94	98	100
Davies *et al*[23]	PSV ratio > 2·0	65	97	97	94	98	96	100
Vashist *et al*[24]	PSV ratio > 2·0	20	—	—	—	—	100	92
Allard *et al*[30]	PSV ratio > 2·0	99	—	—	—	—	87	93
Pooled (95 per cent c.i.)			95 (85–99)	96 (90–99)	95 (84–100)	96 (89–99)	80 (74–85)	96 (94–98)
Infragenicular								
Level 1								
Koennecke *et al*[10]	PSV ratio > 2·0¶¶	49	—	—	73	95	94	91
Moneta *et al.*[13]	No flow	286	—	—	73	91	—	—
Hatsukami *et al.*[14]	Waveform††	58‡‡	—	—	87	100	78	79
Pooled (95 per cent c.i.)					74 (66–81)	93 (87–97)	83 (59–96)	84 (69–93)

n, number of limbs. *Or no signal in case of occlusion; †or peak systolic velocity (PSV) greater than 200 cm/s; ‡or spectral broadening or monophasic waveform in case of greater than 50 per cent stenosis; ¶61 patients, 921 (96 per cent) of 960 segments adequately visualized, §or narrowing of transverse lumen with colour Doppler or a combination, **and waveform change from triphasic to monophasic, or PSV greater than 200 cm/s, ††occlusion, no flow, present collaterals, greater than 50 per cent stenosis; no triphasic signal, poststenotic turbulence or bruit; ‡‡29 patients, 928 segments, 292 excluded for various reasons; ¶¶no specification of grade of stenosis or equal to 50 per cent (*Table 2*). At level 1 homogeneity among studies for sensitivity ($P=0\cdot52$) and specificity ($P=1\cdot0$) could not be rejected, leading to a pooled (95 per cent c.i.) sensitivity of 82 (67–92) per cent and specificity of 96 (93–98) per cent. At level 2 sensitivity ($P=0\cdot47$) and specificity ($P=0\cdot50$) were also homogeneous; pooled (95 per cent c.i.) estimates were 95 (85–99) per cent and 96 (90–99) per cent for sensitivity and specificity respectively. From the same studies accuracy of detection of an occlusion was estimated (*Table 2*). Heterogeneity of sensitivity and specificity among level 1 studies could not be demonstrated ($P=0\cdot69$ and $P=0\cdot37$ respectively), yielding pooled (95 per cent c.i.) estimates of 90 (80–96) per cent for sensitivity and 97 (94–99) per cent for specificity. Raw data of level 2 studies were pooled ($P=1\cdot0$ for both sensitivity and specificity), giving a sensitivity of 95 (84–100) per cent and 96 (89–99) per cent for specificity. Five more studies[13,16,21,24,30] provided raw data on detection of a diameter reduction greater than or equal to 50 per cent, occlusions included (*Table 2*). Sensitivity and specificity were homogeneous among level 1 studies ($P=0\cdot27$ and $P=0\cdot23$ respectively). Pooled (95 per cent c.i.) estimates were 80 (70–87) per cent and 98 (95–99) per cent for sensitivity and specificity respectively. Among level 2 studies sensitivity was heterogeneous ($P=0\cdot005$). Spearman correlation of the sensitivity and (100-specificity) was $-0\cdot67$, indicating concordance in duplex criteria. Four studies[16,21,24,30] could be pooled as among these sensitivity and specificity were homogeneous ($P=0\cdot36$ and $P=0\cdot23$ respectively), resulting in a sensitivity of 80 (71–86) per cent and 95 (90–98) per cent for specificity. Pooling data of level 1[10,11,13,14] and 2[16,21,24,30] studies resulted in sensitivity of 80 (74–85) per cent and 96 (94–98) per cent specificity.

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†Details on raw data can be provided by the authors

Infragenicular arteries

Few studies evaluated duplex scanning of the infragenicular arteries and all were rated level 1. Three studies[10,13,14] provided raw data on detection of an occlusion (*Table 2*) with homogeneous estimates of sensitivity ($P=0\cdot73$) and specificity ($P=0\cdot14$). The resulting pooled (95 per cent c.i.) sensitivity was 74 (66–81) per cent at a specificity of 93 (87–97) per cent. Two studies[10,14] provided data on detection of a stenosis greater than or equal to 50 per cent or an occlusion (*Table 2*). Despite different test criteria heterogeneity of sensitivity and specificity could not be demonstrated ($P=0\cdot34$ and $P=0\cdot28$ respectively). Pooled (95 per cent c.i.) estimates were 83 (59–96) per cent for sensitivity and 84 (69–93) per cent for specificity (*Table 2*).

Discussion

The purpose of this study was to evaluate the diagnostic accuracy of duplex scanning for assessment of arterial occlusive disease in the lower extremity, in methodologically sound studies. In studies considered suitable for quantitative analysis, accuracy of duplex scanning for the respective vascular segments was in the same range, despite the use of different criteria for detection of a stenosis greater than or equal to 50 per cent. The homogeneity of sensitivity and specificity among studies indicates that duplex scanning is reproducible in different study centres in patients with claudication and critical ischaemia. The heterogeneity of sensitivity for detection of a stenosis greater than or equal to 50 per cent or occlusion in the femoropopliteal tract among level 2 studies could not be explained by differences in diagnostic criteria or duplex technique, but was probably due to the different aims of the studies and, as a consequence, the composition of patient collectives. Whereas four studies[16,21,24,30] determined accuracy of duplex scanning for localization and characterization of atherosclerotic lesions, Whyman[22] *et al.* and Davies *et al.*[23] used duplex scanning explicitly to identify lesions in the superficial femoral artery suitable for percutaneous transluminal angioplasty (PTA) on clinical examination.

The meta-analysis shows that duplex scanning is an accurate non-invasive test for assessment of arterial occlusive disease in the aortoiliac and femoropopliteal tract in patients with claudication or critical ischaemia. There was no difference in the accuracy of duplex scanning to detect a significant stenosis or occlusion. This implies that duplex scanning has the potential to replace angiography for determination of treatment strategy, especially in patients with localized lesions as these can be treated by PTA[22–24,40,43,44]. Although diagnostic angiography can be combined with PTA in the same session, duplicate angiography is not uncommon. This increases the complication rate and is inconvenient for the patient. As duplex scanning has a high negative predictive value, significant lesions in the aortoiliac and femoropopliteal tract can be reliably excluded. This may help reduce the number of diagnostic angiographies in patients with symptoms not justifying a surgical or endovascular procedure.

For planning operative treatment most surgeons will feel that diagnostic angiography is still mandatory, especially when the patient needs a femorodistal reconstruction. In these patients assessment of the outflow tract quality (i.e. the cruropedal arteries) is of paramount importance to choose the distal anastomosis site and to predict operation success. Because of the small number of patients studied and the resulting wide confidence intervals of the pooled sensitivity ((95 per cent c.i.) of 83 (59–96) per cent) and specificity of 84 (69–93) per cent) for detection of haemodynamically significant lesions in the below-knee arteries, reliable clinical decisions regarding surgical treatment cannot be based on duplex scanning alone and angiography remains a prerequisite. Further research is warranted to determine the significance of duplex scanning in the evaluation of the distal outflow tract. Alternatives for non-invasive detection of run-off vessels like pulse generated run-off[45,46] and magnetic resonance imaging[36,47,48] have been suggested, but have as yet not found widespread application.

In the University of Amsterdam the integrated use of duplex scanning has significantly reduced the need for diagnostic angiography. The majority of patients with localized lesions are directly scheduled for PTA based on the information from the non-invasive work-up and in selected cases (such as isolated external and/or common iliac artery occlusions) reconstructions are performed without complementary angiography. Elsman *et al.*[44] evaluated a similar strategy in a prospective study of 112 consecutive patients. In the majority of patients treatment strategy could be determined based on the non-invasive work-up, reducing the need for diagnostic angiographies by 50 per cent.

Duplex scanning is an excellent tool in the non-invasive work-up of patients with arterial occlusive disease in the aortoiliac and femoropopliteal tract and because of its high diagnostic accuracy can replace routine diagnostic angiography for planning surgical intervention or PTA in a substantial number of patients. For assessment of the crural arteries angiography remains a prerequisite.

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Experimental autotransplantation of the parathyroid gland

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The lateral parathyroid gland of the rabbit was resected and autotransplanted under an ear skin flap. A skin flap at the opposite side was used as control. The success of autotransplantation was established by microangiography of the transplant and by measuring plasma concentrations of parathyroid hormone (PTH), calcium and phosphorus. After 4 months the animals were killed and the transplant was studied histologically and by electron microscopy. Fourteen animals were included in the study. There was an increase in PTH derived from the transplanted gland after 4–6 postoperative days. All animals developed hypocalcaemia during the 3 days after transplantation. There were no significant changes in serum phosphorus. Transplantation did not alter the morphology of the distribution of the cells in the transplanted gland, which functioned normally after the fourth postoperative day.

Postoperative hypocalcaemia was originally described by Weiss[1] and the rate of clinical hypoparathyroidism varies between 11 and 48·5 per cent after total thyroidectomy[2,3], 0–13 per cent after partial thyroidectomy[4,5] and 2–24 per cent after parathyroid surgery[6].

Autotransplantation of the parathyroid gland into muscle to avoid postoperative hypoparathyroidism was first carried out by Halsted[7]. Parathyroid transplantation is widely used after radical surgery and in the management of primary and secondary hyperparathyroidism[8–10].

This study examined autotransplanted parathyroid tissue to define the time lag between transplantation and complete restoration of function. Changes in the proportion of the cellular population and alterations of cellular architecture were also studied.

Materials and methods

Fifteen male and five female rabbits weighing 3·5–5 kg, on a steady concentration of dietary calcium, phosphorus, proteins and vitamins, were studied.

The animals were anaesthetized with intramuscular injection of Lorazepam (Hypnorm Vet; Leo, Ballerup, Denmark) 0·3 ml per kg body-weight. The two lateral parathyroid glands were excised and preserved until transplanted under a skin flap near the marginal vessels of the rabbit's ear. Another skin flap of the same size was created in the other ear to compare any observed vascular changes at the transplantation site. In ten animals both lateral parathyroid glands were transplanted intact (dimensions 1 × 2 × 1 mm) and in ten each gland was divided in four pieces (dimensions 0·5 × 1 × 0·5 mm).

The function of the graft was assessed by measurement of parathyroid hormone (PTH), calcium and phosphorus levels in blood samples from the vein draining the transplanted parathyroid tissue (usually the marginal vein). PTH was determined by the C-terminal iodine-125 radioimmunoassay (Karolinska Institute, Stockholm, Sweden). The level of PTH in these samples was compared with the concentration in the marginal vein of the opposite ear. Two samples were taken on the 2 days before transplantation to assess the normal values of these parameters. Postoperative blood samples were taken on days 2, 3, 4, 5, 6, 8, 10, 15, 20, 30, 60 and 120.

The development of new vessels revascularizing the graft was studied by microradiography, which involved catheterization of the middle branch of the posterior auricular artery with a small catheter of 0·97-mm diameter with intra-arterial injection of 2–3 ml metrizamide (Amipaque; Winthrop, New York, New York, USA). Magnified radiographs were obtained on days 2, 4, 6, 7, 10, 15, 20, 30 and 40 after transplantation.

The animals were killed 4 months after transplantation and the transplants studied histologically by electron microscopy (in six animals). Blood vessel histology was studied to assess the effect of contrast media and X-rays on the endothelium. The procedures were carried out in accordance with the Helsinki Declaration of 1975.

Results

Three rabbits died in the early stages of the experiment due to uncontrolled gastroenteritis and in three the transplanted tissue was necrosed as a result of wound infection. In 14 animals the transplantation was successful: in nine the lateral parathyroid glands were transplanted intact and in five they were divided into small pieces.

Body-weight

In all 14 animals there was an initial decrease of 10 per cent of body-weight 2 weeks after transplantation. By the fourth postoperative week body-weight started to increase and reached the preoperative levels by the 12th postoperative week.

Secretion of parathyroid hormone

The level of PTH in the blood from the graft ear started to increase by 4–6 days after operation and remained significantly higher than systemic concentrations throughout the follow-up period (*Fig. 1*).

Blood level calcium and phosphorus

Significant hypocalcaemia was observed in the group on post-transplant days 2 (mean(s.e.m.) calcium concentration 2·36(0·08) mmol/l), 3 (2·18(0·11) mmol/l) and 4 (2·25(0·07) mmol/l). Six days after surgery the plasma calcium level was restored to normal. There were no significant changes in serum phosphorus concentration.

Microangiographic study of the transplant

During days 2–4 after transplantation all pre-existing blood vessels at the centre of the graft disappeared, while

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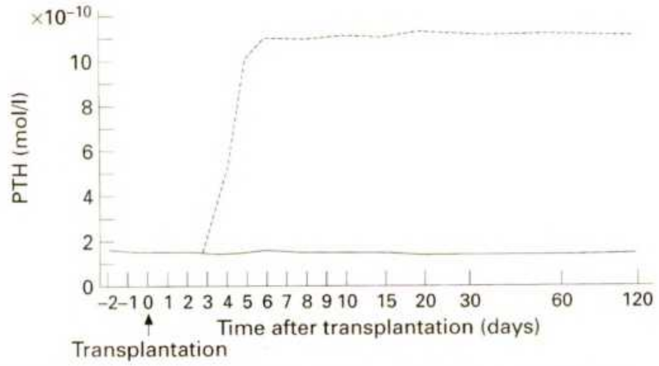

Fig. 1 Changes of the level of parathyroid hormone (PTH) from the grafted ear (-----) and in the systemic circulation (———) of the 14 rabbits

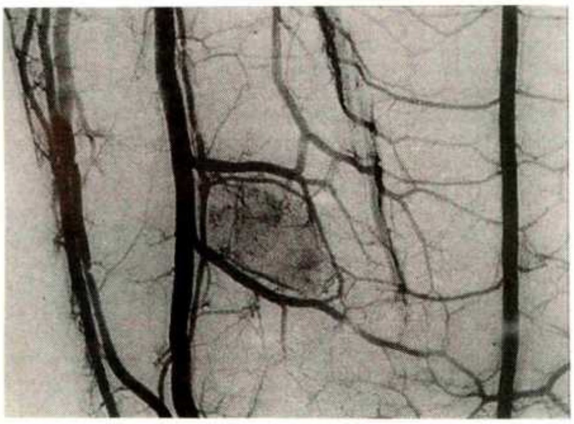

Fig. 2 Microangiogram of the graft on day 7 following transplantation. Note the development of sinusoids

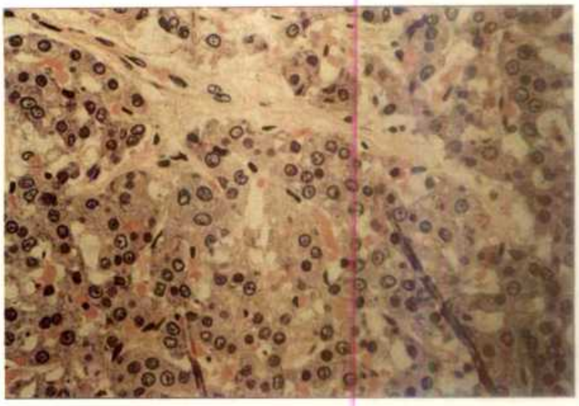

Fig. 3 Histological appearance of the graft 5 months after transplantation. The parenchyme is divided into lobules by fibrous tissue trabeculae rich in blood vessels

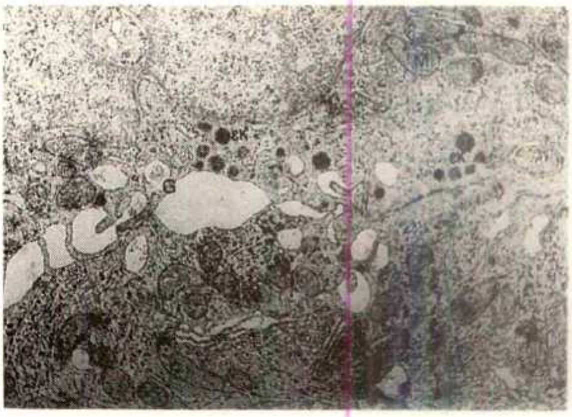

Fig. 4 Electron micrograph of the graft 5 months after transplantation. G, Golgi apparatus; εK, secreting granules; M, mitochondria

in the periphery a rich network of pre-existing and newly formed blood vessels was observed. By the end of the first week these vascular changes were complete, and sinusoids developed which drained the graft (*Fig. 2*). After the third postoperative week the sinusoids were straightened and new vessels formed.

Histology of the transplanted parathyroid gland

In all animals the graft was found between cartilage and skin. The transplanted gland showed trabeculae from connective tissue which were dividing the gland into lobules. The vessels of these trabeculae showed well developed sinusoids (*Fig. 3*).

At the periphery of the transplanted gland in ten of 14 animals there was a zone of cells with large nuclei and small amounts of cytoplasm, which probably represented regenerating parathyroid cells.

In four of the animals in which the parathyroid gland was transplanted intact, the central region of the graft showed fibrosis, infiltration, a lymphocytic inflammatory reaction and central necrosis of 50 per cent. This degeneration was due to inadequate blood supply of the central region. The periphery of the gland, however, had normal cellular structure with well developed trabeculae and sinusoids.

Of the cellular population of the parenchyma 80–85 per cent was made up of principal cells in which the cytoplasm was granular and slightly basophilic with prominent Golgi apparatus (*Fig. 4*). The remaining 15–20 per cent of the cells were of small size, with coarser cytoplasm and dark nuclei of various sizes. The cells had a well developed endoplasmic reticulum with multiple free ribosomes and mitochondria, an active Golgi apparatus and few lysosomes. Secretory and glycogen granules were also observed (*Fig. 4*).

None of the 14 animals showed endothelial damage from the contrast media.

Discussion

The time to return to functional activity of transplanted parathyroid tissue is not well defined. Hickey and Samaan[11] transplanted parathyroid tissue into the muscles of the forearm and detected high levels of PTH after the third postoperative day. This was thought to be due to leakage of stored hormone and not active production of PTH from the graft. At that stage the transplanted gland was not likely to be revascularized.

In the present study the level of PTH in the blood was combined with an angiographic study to define the time of revascularization of the graft. The rabbit's ear was chosen since it has a rich vascular bed suitable for multiple venepuncture and microradiographic studies. The early vascular changes observed between 2 and 4 days after transplantation were due to an inflammatory reaction and included development of a dense vascular bed. This traumatic inflammatory reaction has been described previously[12,13] and was probably irrelevant to the procedure of graft revascularization since similar vascular changes were observed in the control skin flaps. After the sixth post-transplantation day sinusoids were observed which were either retained or which became gradually elongated and transformed to new vessels. The sixth post-transplantation day when the graft was revascularized coincided with active production of PTH.

In all animals there was a decrease in the plasma calcium concentration immediately after lateral parathyroidectomy, although the medial parathyroids were intact. Normal calcium levels were completely restored between 4 and 6 days after operation. Hypocalcaemia resulted from dysfunction of the medial parathyroid glands as a result of trauma or excision of the lateral parathyroids, which are the main regulators of calcium homoeostasis in the rabbit[14]. The latter theory is the most probable explanation of the observed hypocalcaemia[15].

Whether the gland is implanted intact or in pieces, the transplantation was successful, as shown by postoperative levels of PTH. In the four animals with an intact gland, central necrosis of 50 per cent was observed. Until the graft becomes fully revascularized its nutrition is dependent on the diffusion of substances from the periphery[16,17]. The size of the lateral parathyroid gland in the rabbit is 1 × 2 × 1 mm and transplantation of tissue of a larger size may lead to central necrosis, resulting in destruction of the whole graft. In human transplantation the graft should be divided into pieces with a dimension of no more than 1 × 1 × 3 mm. The human parathyroid gland is larger than that of the rabbit[18]. Transplantation of 40–60 mg parathyroid tissue is sufficient to maintain calcium and phosphorus homoeostasis in humans[18].

Histological studies confirmed that the transplanted parathyroid tissue was normal, having a lobular structure and sinusoids between the lobules. These sinusoids were outlined in the arteriograms. Electron microscopic studies proved that most cells were in the active phases III and IV[18] and therefore remained functionally active, producing PTH.

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Surgical workshop

Simple and reliable technique for local resection of early gastric cancer

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There has been an increase in the number of recognized early gastric cancers with the recent advance in diagnostic modalities[1]. In some cases, less aggressive procedures are indicated and local resection, with or without limited lymph node dissection, is one of the treatments of choice. It is, however, sometimes difficult to ensure adequate excision with tumour-free margins because such lesions are movable and may not be firmly fixed to the muscle layer. A simple technique to determine the sites to be incised to allow adequate resection of the tumorous lesion with ease and safety is reported here.

Surgical technique

The lesion to which this technique relates is an early gastric tumour that cannot be treated endoscopically, is up to 3 cm in diameter and largely limited to the submucosal layer. It may be revealed by radiography, endoscopic examination, or endosonography.

Two or 3 days before operation, under endoscopic examination, India ink is injected into the submucosal layer around the lesion at four or five points on the line to be incised. At laparotomy, the anterior wall of the stomach is incised horizontally or obliquely for about 5 cm in length, an adequate distance being maintained from the lesion to be resected. The points of India ink previously injected are confirmed macroscopically. Intravenous catheters (Surflo; Terumo, Tokyo, Japan) are inserted at the previously dyed points so that the lesion is fixed firmly. The inner needles are removed, leaving the catheters penetrating the gastric wall, in order that other organs or tissues around them are not injured. The catheters through the gastric wall provide guidance for resection of the lesion using electric cautery from point to point; this results in adequate margins (*Fig. 1*). This technique allows the mucosal layer to be incised accurately with the serosal and muscle layers. The resulting gastric wall defect, from resection of the lesion as well as the initial incision, is closed in the conventional manner or using a suture device. If the lesion is located on the posterior wall, the gastrocolic ligament should be incised. Lesions of the greater or lesser curvatures may be treated in an analogous fashion. Level 1 nodes are dissected when poorly differentiated adenocarcinoma or signet-ring cell carcinoma is diagnosed before operation, or if there is infiltration in to the submucosal layer.

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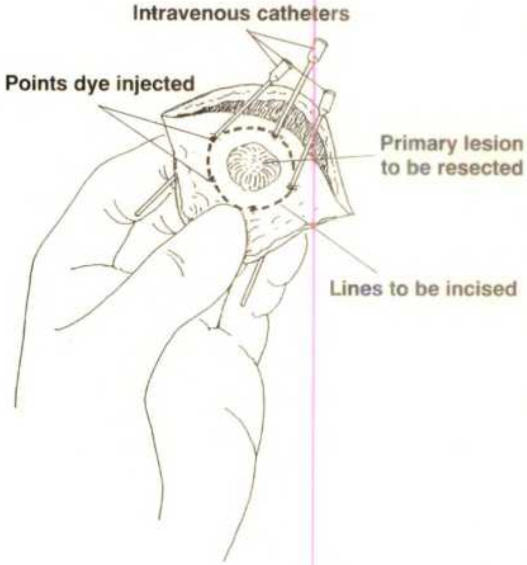

Fig. 1 Intravenous catheters are inserted through the gastric wall at points previously marked from inside the stomach after incision of the anterior wall. The gastric wall is incised by electric cautery along the lines connecting the points, using the catheters for guidance

Table 1 Patients with gastric cancer treated with local resection using this technique

			Lesion						
Patient no.	Age (years)	Sex	Location	Size (cm)	Gross finding	Histology	Depth*	Margins from the lesion (max./min.) (cm)	Operative duration (min)
1	83	F	Lower third Greater curve/ Posterior	0·7 × 0·5	Depressed	Well differentiated adenocarcinoma	Mucosal layer	2·5/1·7	74
2	74	M	Middle third Lesser curve	2·4 × 1·5	Elevated	Poorly differentiated adenocarcinoma	Submucosal layer	1·8/2·8	78
3	78	F	Lower third Anterior	2·5 × 2·2	Depressed	Well differentiated adenocarcinoma	Mucosal layer	2·5/3·0	60

*Depth of lesion was histologically confirmed

The authors have successfully treated three patients with early gastric cancer using this easy technique (*Table 1*).

Discussion

Early detection of malignant gastric lesions has made operations less aggressive, especially when the lesion is limited to the mucosal or submucosal layer without lymph node involvement[1]. Local resection is one of the treatments of choice for early lesions, along with laparoscopic assisted or endoscopic resection[2]. The authors perform local resection in patients with early gastric tumours that cannot be treated endoscopically and are up to 3 cm in diameter, except in those with massive submucosal infiltration, especially in the elderly or poor-risk patients.

Following local resection, margins should be confirmed as free from tumorous tissue. Locally resected lesions are, however, not often fixed to the muscle layer (unless there are coexisting scars), resulting in difficulty in incision along appropriate lines with adequate margins. The shape of the resected part of the mucosal layer is sometimes different from that of the muscle layer, suggesting that the mucosal region is not resected exactly as planned. In cases of massive involvement of the submucosal layer, revealed histologically, further radical operation should be performed.

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Intestinal glycosaminoglycans in neonatal necrotizing enterocolitis

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Advanced necrotizing enterocolitis (NEC) is a common neonatal surgical emergency of unknown aetiology. Despite improvements in the prognosis, the aggressive form of the disease is still associated with significant rates of morbidity and mortality. Recent evidence indicates that the extracellular matrix (ECM) is important in gastrointestinal development and glycosaminoglycans, major constituents of the ECM, are attenuated in inflammatory bowel disease. The hypothesis of this study was that changes in the nature and distribution of intestinal glycosaminoglycans occur in NEC. The distribution and nature of glycosaminoglycans were determined in 31 sections of well preserved resection margins and severely diseased bowel from eight neonates affected by NEC. An established histological method of glycosaminoglycans analysis using cationic gold with silver enhancement was employed in this study. The identity of specific glycosaminoglycans was also elucidated using a combination of cationic gold staining and glycanase digestion. In well preserved tissue, staining was seen throughout the full thickness of the bowel. The epithelial basement membrane and basolateral surfaces, lamina propria and submucosa were particularly prominent. In moderate disease, patchy loss of anionic sites was frequently observed with glycosaminoglycans-deficient areas adjacent to intact sites. In severe NEC, there was extensive loss of glycosaminoglycans in most of the sections examined. Glycanase analysis revealed that the glycosaminoglycans in well preserved tissue were sensitive to chondroitinase ABC and only vascular sites were sensitive to heparinase III. The consequences of glycosaminoglycans loss in NEC as demonstrated in this study are not known but modulation of gastrointestinal glycosaminoglycans could be important in the pathogenesis of NEC and may underlie some of the clinical manifestations of this condition.

Necrotizing enterocolitis (NEC) is an inflammatory condition of the gastrointestinal tract which usually develops in the neonatal period. The aetiology is unknown but prematurity is a risk factor. The majority of affected babies improve with non-operative management but up to a third develop complications that require laparotomy, making NEC the most common surgical emergency in neonates[1]. Laparotomy carries a mortality rate of 20–50 per cent with long-term morbidity in up to half of the survivors[1–3].

Two subgroups of patients with NEC can be identified. The first have localized disease, few constitutional manifestations and respond well to medical treatment or localized resection[4]. The second group generally have more extensive and severe disease, often with systemic complications including hypotension, hypoalbuminaemia and disseminated intravascular coagulation. While there have been improvements in the prognosis, the pathophysiological mechanisms operating in NEC remain largely speculative. Recently it has been shown that the sulphated glycosaminoglycans – heparan sulphate, dermatan sulphate and chondroitin sulphate – are widely distributed within normal intestine[5]. Glycosaminoglycans consist of disaccharides in repeating sequence and are usually bound to core proteins as proteoglycans. They are found inside cells, on cell surfaces and bound to other extracellular matrix (ECM) components. Glycosaminoglycans are considered to be important in structural integrity, epithelial membrane and vascular permeability, cellular traffic, bacterial and macrophage adhesion, macromolecular localization, cellular proliferation and cell-to-cell adhesion[6]. In view of their physiological importance, it has been proposed that modulation of intestinal glycosaminoglycans may underlie many of the pathological features of intestinal inflammation[5]. The distribution of gastrointestinal glycosaminoglycans in NEC has been examined using a histochemical technique in this report.

Materials and methods

Resected bowel was obtained from eight patients who had surgery for NEC. The mean gestational age was 33 (range 27–38) weeks and mean birth weight 1684 (range 705–2908) g. Age at the time of surgery ranged from 2 to 62 days. Collected samples were handled in standard fashion, placed in 10 per cent formalin after operation, embedded in paraffin and 3-μm sections prepared. Thirty-one tissue sections were stained and examined to compare areas of severe NEC with resection margins. In view of the difficulties of obtaining normal neonatal bowel, five well preserved samples from resection margins were used as controls.

Histological examination

Paraffin sections were dewaxed and glycosaminoglycans were detected using a cationic gold (CG) method as previously described[7]. Briefly, a 5-nm gold-conjugated poly-L-lysine probe (Biocell Research Laboratories, Cardiff, UK) was applied to each slide at a pH of 1·5. After 60 min in a humid environment the slides were washed in deionized water and developed with a silver enhancer (Biocell Research Laboratories) for 10 min. Meyers haematoxylin was used as a counterstain and the slides were mounted with Aquamount (BDH, Essex, UK). Sections from the same blocks were also stained with haematoxylin and eosin for comparison.

Enzymatic digestion

The nature of the glycosaminoglycans at the resection margins and in diseased tissue was studied using specific glycanases. Sections were incubated for 4 h with chondroitinase ABC or heparinase III (Sigma, Dorset, UK)[7]. Control sections from the

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same tissue blocks were incubated with phosphate-buffered saline (PBS) for 4 h. Following washing with PBS, the CG stain was then carried out as described above.

Quantification

Histological examination was carried out using an Olympus BH-2 light microscope. A scoring system for assessing disease severity on standard sections stained with haematoxylin and eosin of experimentally induced NEC in neonatal piglets has previously been described[8]. The variables used were vessel engorgement, mucosal sloughing, necrosis, ulceration, perforation, pneumatosis-like lymphatic dilatation and pneumatosis intestinalis. Each variable was scored on a scale of 1 to 5. For the purpose of this study, the scoring system was modified by considering each bowel section in four layers. The epithelium, lamina propria and muscularis mucosa, submucosa and muscle were scored separately. The number of variables in each layer was reduced from five to four. In sections stained with haematoxylin and eosin, a score of 0 was given for normal appearance, 1 for mild, 2 for moderate and 3 for severe changes in each layer. On sections stained with CG, corresponding layers were examined and similarly scored on a scale of 0–3 to quantify the presence and intensity of glycosaminoglycans staining. A score of 0 represented intact distribution and normal intensity and 3 an absence of glycosaminoglycans. The same criteria were used to analyse sections stained following enzymatic digestion of glycosaminoglycans. The maximum score indicating the most severe disease with both haematoxylin and eosin and CG staining was 12.

Results

Glycosaminoglycans distribution in well preserved neonatal bowel

On the basis of haematoxylin and eosin staining, the 31 sections were divided into severe, moderate and well preserved categories as follows: severe (score 9–12) $n = 17$, moderate (score 5–8) $n = 9$, well preserved (score 4 or less) $n = 5$. The five sections in the well preserved group showed little evidence of NEC on haematoxylin and eosin staining; the architecture was well preserved, there were few inflammatory cells and little evidence of vessel dilatation or haemorrhage. They were used as controls and analysed for the distribution of glycosaminoglycans as described above. This was taken as an approximation of the situation in healthy neonatal bowel.

All layers of the bowel were stained (*Table 1*). In the epithelial layer, staining was most prominent in the basement membrane and basolateral surface (*Fig. 1*). An epithelial lining of CG was occasionally observed and goblet cells stained frequently. *Fig. 1* also shows CG staining in the lamina propria with a network of fine interlacing strands probably representing vascular glycosaminoglycans. In the submucosa the staining pattern was intense and predominantly associated with the collagen matrix (*Fig. 2*). Medium and large vessels were also heavily stained with CG deposited on the endothelial basement membrane, smooth muscle cells and perivascular region (*Fig. 2*).

Glycosaminoglycans distribution in diseased bowel

Sections of severe NEC stained with haematoxylin and eosin were characterized by mucosal ulceration and stripping, inflammatory infiltrates and necrosis. These were all scored at between 9 and 12. Generally, NEC severity was mirrored by an increase in glycosaminoglycans loss. The basolateral and basement

Table 1 Glycosaminoglycans distribution in neonatal intestine: light microscopy results using a cationic gold stain at pH 1·5

Site	Well preserved intestine (score ≤ 4)	Severely diseased intestine (score 9–12)
Epithelial surface covering	+	+ +
Nucleus	+ +	+ +
Basolateral surface	+ + +	–
Epithelial basement membrane	+ + +	–
Lamina propria	+ + +	+
Submucosa	+ + +	+
Smooth muscle cells	+ + +	+ +

–, Absent; +, occasionally present/severely attenuated; + +, commonly present/moderately attenuated; + + +, consistently present/intact

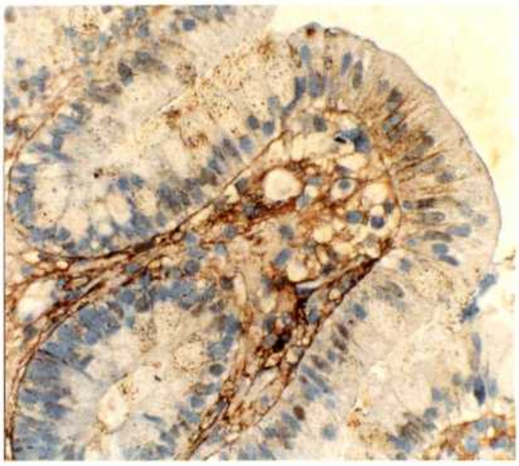

Fig. 1 Photomicrograph of colonic resection margin of a patient affected by necrotizing enterocolitis showing cationic gold (CG) deposited in the basement membrane, basolateral epithelial surfaces and lamina propria (CG stain; original magnification ×40)

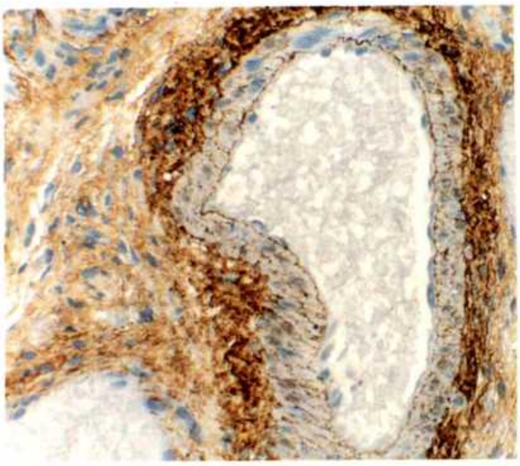

Fig. 2 Photomicrograph centred on the submucosa of a well preserved neonatal colonic section. A large submucosal vessel with an intense perivascular stain and intact surrounding cationic gold (CG) deposition is demonstrated (CG stain; original magnification ×40)

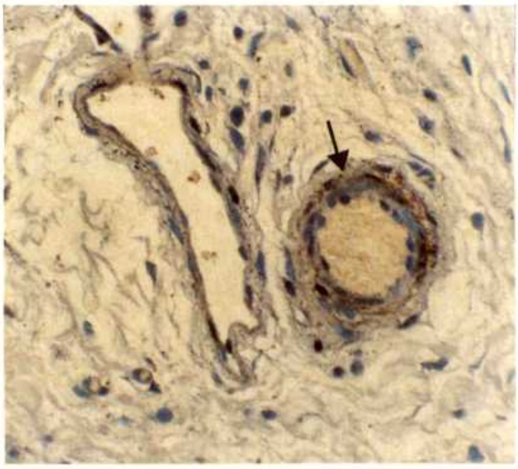

Fig. 3 Severe necrotizing enterocolitis in neonatal colon with widespread disruption of submucosal anionic sites but limited preservation of vascular glycosaminoglycans (arrow) (cationic gold stain; original magnification ×40)

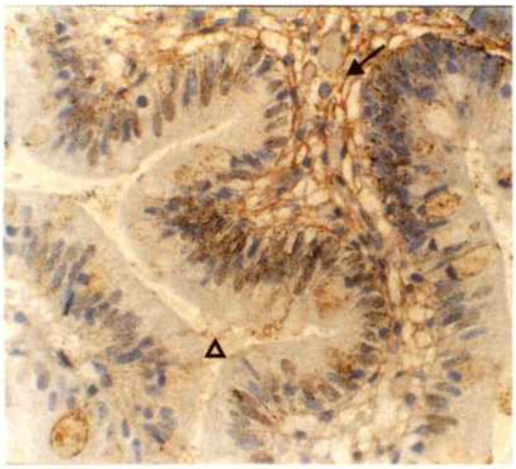

Fig. 4 Moderate necrotizing enterocolitis with patchy cationic gold (CG) staining. Arrow shows well preserved glycosaminoglycans. Arrowhead shows adjacent area of attenuation (CG stain; original magnification ×40)

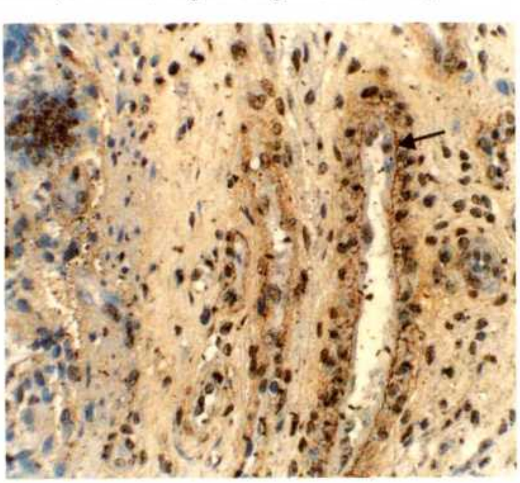

Fig. 5 Photomicrograph of neonatal colon following incubation with Chondroitinase ABC showing preservation of vascular glycosaminoglycans (arrow) and digestion of surrounding anionic sites (cationic gold stain; original magnification ×40)

membrane glycosaminoglycans in these sections were attenuated in all samples. The submucosa was similarly affected in the most severe cases (*Fig. 3*). In sections with moderate evidence of disease on haematoxylin and eosin staining (score of 5–8) and no loss of anatomical integrity in the epithelial layer, the glycosaminoglycans staining was variable, with deficient areas often adjacent to intact sites (*Fig. 4*). In addition, there was sometimes a disparity between haematoxylin and eosin and CG staining with a tendency for a greater attenuation of glycosaminoglycans than might have been suggested on examination using haematoxylin and eosin.

Nature of glycosaminoglycans in neonatal bowel

To elucidate the nature of glycosaminoglycans in neonatal bowel, specific glycanases were employed. When chondroitinase ABC was applied, the glycosaminoglycans in all layers of the bowel wall were digested, leaving the vascular stain intact (*Fig. 5*). Some of the similarities between the chondroitinase-digested bowel (*Fig. 5*) and the appearance of submucosal loss in *Fig. 3* are striking. While vascular glycosaminoglycans were reduced with heparinase III, epithelial basement membrane and basolateral glycosaminoglycans were largely unaffected.

Discussion

Evidence is growing that the ECM is structurally and functionally important in the gastrointestinal tract. Much of the work has concentrated on the glycoprotein components of the ECM but recent reports have highlighted the importance of glycosaminoglycans in gastrointestinal development and inflammatory gut disorders[9–11]. There are few detailed reports of the nature and distribution of glycosaminoglycans in paediatric and adult bowel, and no published descriptions of them in human neonatal intestine. A major reason for this is the difficulty in obtaining normal gastrointestinal tissue in neonates. In this study minimally diseased resection margins were selected as an approximation of normality. Using a CG probe technique, originally described for electron microscopy by Skutelsky and Roth in 1986[12], later modified for light microscopy[7], paraffin sections of neonatal bowel from babies with NEC were examined.

The absence of data on the distribution of glycosaminoglycans in human neonatal bowel makes comparisons difficult. However, in well preserved tissue glycosaminoglycans were found to be distributed in all layers of the bowel. In common with those in older children and adults, basolateral, epithelial surface, basement membrane, submucosal and muscle glycosaminoglycans were particularly prominent[5]. These findings are also similar to those described by Dikranian and colleagues[13] in a CG study of normal rat colon. In contrast to the pattern seen in well preserved tissue, CG deposition was markedly reduced in all layers in severe disease. In sections demonstrating moderate disease as judged from haematoxylin and eosin sections, epithelial and lamina propria glycosaminoglycans distribution was frequently patchy with areas of attenuation adjacent to well preserved CG sites. These observations are interesting in the light of microscopic evidence of the patchy distribution of inflammation in NEC[14].

Investigation of the cause of the glycosaminoglycans disruption was not the purpose of this study. Many mechanisms are known to influence glycosaminoglycans distribution and metabolism. Inflammatory cytokines, proteases and glycanases, released from inflammatory cells, have all been shown to attenuate tissue glycosaminoglycans[15]. These mechanisms are thought to be responsible for the loss of glycosaminoglycans seen in inflammatory bowel disease. Murch and colleagues[5] showed that in ulcerative colitis and Crohn's disease, inflammation was accompanied by a loss of glycosaminoglycans staining and was most severe in areas of marked inflammatory cell infiltration. Similar mechanisms may be operating in NEC.

Recent research has highlighted the importance of intestinal maturation in the pathogenesis of NEC[16,17]. The ECM in particular is thought to be critical in gastrointestinal development. In animal studies of epithelial–mesenchymal interactions, Simon-Assmann and colleagues have recently shown that heparan sulphate is essential for regulating cell behaviour during morphogenesis[11]. Interestingly, in this study, although the distribution of neonatal glycosaminoglycans was similar to that seen in children and adults, the nature of glycosaminoglycans identified in well preserved tissue was found to be different. In contrast to that in older children and adults, it was found that the CG staining of the basement membrane was not affected by heparinase III but was markedly reduced by chondroitinase ABC. The possibility exists that neonatal bowel may have an ECM profile which differs from that of older children and adults and may be more susceptible to the factors that result in NEC, a hypothesis which is currently being investigated in this department.

The consequences of the loss of glycosaminoglycans observed in this study are not known. However, there are now a number of reports that show that loss of glycosaminoglycans is associated with increased permeability to proteins. This has been extensively investigated in the kidney[18,19], bladder epithelium[20] and in endothelial monolayers[21]. It may also be of physiological importance in NEC. In this regard it may be pertinent that glycosaminoglycans were invariably diminished in the epithelial intercellular spaces, which are known to be important sites for regulating transmucosal fluid fluxes and protein transport in the gastrointestinal tract[22,23]. Alterations in other glycosaminoglycans functions such as structural integrity, cellular traffic, growth factor binding and thromboresistance may contribute to the clinical picture of NEC. Further investigations into the role of glycosaminoglycans and other ECM components in NEC could provide clues to the aetiological and pathophysiological mechanisms involved in this condition.

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British Journal of Surgery 1996, **83**, 419

Surgical workshop

Subrectus pouch for renal transplantation

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Correct positioning of a renal transplant following implantation and revascularization is a vitally important and sometimes difficult part of the operation. If the renal vessels are, or become, kinked, acute thrombosis may result in graft loss. Kidney transplants are normally positioned in the retroperitoneal space of the iliac fossa, lying in the gutter formed by the iliopsoas muscle (the traditional lateral position)[1,2]. In this position the vessels run medially from the hilum of the kidney and vessel kinking can usually be avoided by rotating the kidney carefully until the correct lie is found. Nevertheless some kidneys are difficult to position in this way and in these cases it is advantageous to place the transplant kidney in a specially fashioned subrectus pouch.

Surgical technique

The subrectus pouch is most easily created before the kidney is implanted but may also be fashioned after revascularization when it is clear that the kidney will not sit well in the traditional position. The muscle layers of the upper leaf of the incision are picked up with strong tissue forceps and elevated. Sharp dissection is used to strip the peritoneum away from the posterior rectus sheath, working in cranial and medial directions towards the level of the umbilicus. This creates a pouch between the peritoneum and rectus sheath which is large enough to accommodate a human kidney (*Fig. 1*). Care must be taken to avoid the inferior epigastric vessels, which may cause troublesome bleeding.

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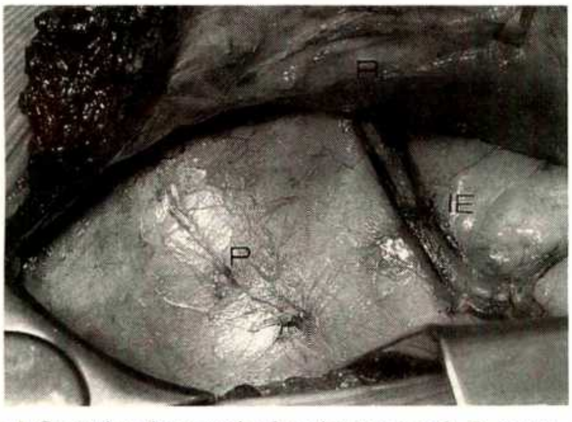

Fig. 1 Operative photograph of a subrectus pouch. R, rectus muscle; P, peritoneum; IE, inferior epigastric vessels

After completion of the anastomoses, the transplant kidney is rolled upwards and medially to lie in the subrectus pouch. This position constitutes a 180° rotation from the traditional lateral position so that the anterior surface of the kidney now lies posteriorly. The renal pelvis faces laterally or inferiorly and the renal vessels run down to the recipient iliac vessels in a gentle C-shaped curve, which prevents kinking.

Discussion

It has been stated that it is advantageous to place the renal pelvis of a transplanted kidney anteriorly so that, if a urological complication develops, subsequent reconstructive surgery is easier[3]. To achieve this, most transplant surgeons place the right kidney in the left iliac fossa and the left kidney in the right iliac fossa. Some surgeons believe this is so important that they deliberately place the transplant kidney upside down to achieve correct orientation of the renal pelvis[3]. In the subrectus pouch the pelvis is anterior when the right kidney is in the right side and the left kidney is in the left side.

This technique was used in 34 (17 per cent) of the authors' last 200 transplants. The rate of early vascular thrombosis during this period was 3 per cent and none occurred in kidneys placed in the subrectus pouch.

This technique has a number of advantages. Its principal use is in positioning a transplant kidney which does not sit naturally in the iliac fossa or where this position causes kinking of the renal vasculature. This may be a particular problem in retransplants when the renal anastomoses may have to be placed closer to the inguinal ligament than is usually desirable. A kidney anastomosed at any point can always be positioned in a subrectus pouch. In addition, kidneys placed in a subrectus pouch are much more superficial than those placed in the iliac fossa, making ultrasonographic images clearer and easier to interpret. In this unit ultrasonographic measurements of transplant cross-sectional area are used as an adjunct in diagnosing acute rejection[4] and this technique is much more reliable in kidneys placed in a subrectus pouch. Finally, because of the superficial position, subrectus pouch kidneys are much easier to biopsy percutaneously.

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British Journal of Surgery 1996, **83**, 420–421

Postoperative thromboembolism after day-case herniorrhaphy

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Thromboembolism is a serious complication of surgery and prophylaxis is therefore recommended. This study examines a new aspect of the problem, the incidence of thromboembolism after day-case surgery. From 1982 to 1992, 2281 patients underwent day-case repair for inguinal hernia management. Hospital admission for thromboembolism within the first 30 days after surgery was identified by computer linkage to the National In-Patient Register, which contains details of all hospital admissions in Denmark. One patient developed non-fatal pulmonary embolism. No other patients were admitted to hospital with venous thromboembolism within 30 days of herniorrhaphy. It is concluded that there is no need for routine prophylaxis for thromboembolism in day-case hernia surgery.

Low-dose heparin is well established in the prevention of postoperative thromboembolic complication after major surgery. However, the risk of thromboembolism after minor surgery also warrants prophylaxis[1].

The period of prophylaxis should ideally include the time after discharge from hospital, because delayed pulmonary embolism may occur within a month after operation[2]. Interestingly, delayed pulmonary embolism is most frequently found after low-risk surgery[2].

Because of the increased use of day-case procedures, this study examines the need for prophylaxis in patients undergoing day-case herniorrhaphy.

Patients and methods

From 1982 to 1992, 2281 patients underwent day-case abdominal hernia repair in the Department of Surgical Gastroenterology, Copenhagen County Hospital in Herlev. Patients with bilateral or recurrent herniation were only included in the study once, at the first operation. The patients did not suffer from co-morbid disease other than the herniation. None of the patients were given any specific prophylaxis against thromboembolic disease.

The surgical procedures were consistent throughout the period of investigation, consisting of posterior wall repair for indirect inguinal hernias and suture of the conjoined tendon to the pubic bone (modified by McVay) for direct inguinal and femoral hernias. Ventral herniotomy was performed by single- or double-layer closure of the fascial defect. The patients were encouraged to walk as much as possible after discharge from hospital.

Details of the sex, age, type of hernia, body mass index and anaesthetic procedure were obtained from the records and entered into a computer database, together with the unique ten-digit personal identification number (PIN) given to every Danish citizen.

The period of risk for development of deep venous thrombosis and/or pulmonary embolism was defined as being from the date of operation until 30 days after surgery.

The patients were traced by their PIN at computer links to the National In-Patient Register for admission for thromboembolism to any hospital in Denmark within the period of risk. Death within the period of risk was registered from the Central Personal Register of Denmark.

The study protocol was approved by the local ethics committee and the Danish Board of Registration Control before the investigation.

The incidence of thromboembolism was calculated with 95 per cent confidence interval. Odds ratios for the registered parameters were determined.

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Table 1 Characteristics of 2281 patients undergoing day-case hernia repair

	Women ($n = 239$)	Men ($n = 2042$)	Total ($n = 2281$)
Median (range) age (years)	41 (16–75)	48 (15–85)	47 (15–85)
Median (range) body mass index	22 (13–41)	24 (14–39)	24 (13–41)
Anaesthesia (%)			
General	87	81	81
Regional	13	19	19
Number of hernias*	259	2170	2429
Diagnoses (%)			
Indirect inguinal	48	59	58
Direct inguinal	17	33	32
Femoral inguinal	11	0	1
Ventral	22	5	7
Others	2	3	2

*Some patients were operated simultaneously for two ($n = 144$) or three ($n = 2$) hernias

Results

Study details are shown in *Table 1*. One case of thromboembolism was identified within the first 30 days after surgery, corresponding to an incidence of 0·04 per cent (1:2281 (95 per cent confidence interval 0·00–0·18)). The patient developed non-fatal pulmonary embolism 27 days after direct inguinal hernia repair. He was a 52-year-old man, weight 82 kg and height 171 cm, operated on under general anaesthesia. No patient died within 30 days after surgery.

Discussion

This study has found a near-zero risk for the development of clinical deep venous thrombosis and pulmonary embolism after day-case abdominal hernia repair. The result is identical to the incidence of pulmonary embolism in the total Danish population[3].

Although a low ratio would be expected for otherwise healthy patients undergoing minor surgery for hernia, these findings are surprising when compared with other series. Huber and colleagues[2] investigated 4590 patients undergoing hernia repair and found 13 cases (0·28 per cent) of pulmonary embolism during the first postoperative month. The increased incidence described by Huber and co-workers could be explained by a higher number of patients at risk of thromboembolism in their study group. However, detailed risk factors are not published for patients suffering from groin hernia. In 1971 Kakkar and colleagues[1] showed that in a group of 27 patients undergoing repair of inguinal hernia 26 per cent developed deep venous thrombosis, as detected by the positive radioactive fibrinogen uptake test. In another group receiving heparin prophylaxis only 4 per cent of the patients developed thrombosis.

The present data are valid because they are based upon the extensive registration of every Danish citizen by a PIN introduced in 1968. The registration is greater than 99·99 per cent. Related registers have been carefully developed under the highest security control in recent decades in Denmark. From 1977 all persons are registered by their PIN in the National In-Patient Register when admitted to a Danish hospital[4]. In addition, a patient suspected of having thromboembolism in Denmark will always be admitted to hospital and thereby included in the National In-Patient Register.

The total incidence of thromboembolism, including subclinical cases, is much higher than the clinical incidence. Subclinical deep venous thrombosis is important because of the impaired venous function that may occur years after the episode[5] and the development of asymptomatic[6] and fatal[7] pulmonary embolism. The incidence of thromboembolism may be underestimated, even in inpatients[3], and some subclinical cases who were not diagnosed and therefore not registered have probably been overlooked in this study.

Age has been considered a risk factor according to a consensus report which identifies patients over the age of 40 years to be at higher risk and to require prophylaxis[8]. This recommendation seems questionable for day-case surgery from the results of this study, on a group who had a median age of 47 years with 78 per cent of the patients being over 40 years old.

Obesity has also been regarded as a risk factor[8] and included in an index of thromboembolism risk[9], but with regard to day-case hernia surgery, obesity does not seem of great importance.

It is concluded that prophylaxis for thromboembolism does not seem necessary for otherwise healthy patients undergoing day-case repair for hernias. It should however be stressed that the study group was considered to be of low risk.

Acknowledgements

Rhône-Poulenc Rorer A/S is acknowledged for financial support.

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Corrigendum

Q. Zhang, D. H. King, A. D. Houghton, M. R. Tyrrell, Y. P. Panayiotopoulos, J. F. Reidy and P. R. Taylor. Non-invasive assessment of arterial disease: a comparison of Quickscan with intra-arterial digital subtraction angiography. *British Journal of Surgery* 1996; 83: 231–234.

The manufacturer of Quickscan is HNE Diagnostics, Cardiff, UK.

Erratum

W. D. C. Kealey, W. A. McCallion, S. Brown, S. R. Potts and V. E. Boston. Midgut volvulus in children. *British Journal of Surgery* 1996; 83: 105–106.

Fig. 1 was printed upside down. The Journal apologizes to authors and readers.

British Journal of Surgery 1996, 83, 422–428

Correspondence

Combined liver transplantation and pancreatoduodenectomy for irresectable hilar bile duct carcinoma

Sir

Dr Cherqui and colleagues (*Br J Surg* 1995; 82: 397–8) described combined liver transplantation and pancreatoduodenectomy for irresectable hilar bile duct carcinoma and reported on two patients who underwent operation in 1992 and probably 1993. The authors stated that, to their knowledge, pancreatoduodenectomy in combination with total hepatectomy and liver transplantation had not been described previously.

May I draw your attention to our article[1] in which we described exactly this combination of total hepatectomy in continuity with partial pancreatoduodenectomy (Whipple's procedure) followed by orthotopic liver transplantation for the treatment of central hilar carcinoma. We then reported our preliminary results in seven patients and, at that time, six successful operations. One patient died from haemorrhage on day 15 after operation and another patient with distant metastases surgically verified died 6 months after liver transplantation from diffuse tumour metastasis. At present we have performed 13 so-called extended bile duct resections and achieved an actuarial 3-year survival rate of 56 per cent.

To describe briefly the surgical rationale of our operation we make two points. First, as in all other tumour surgery, only those with not-too-far advanced tumour stage and without lymph node metastasis have a chance of cure by local surgical excision Therefore, advanced metastasized tumours such as those included by Starzl *et al.*[2] in their cluster series are probably beyond cure by any surgical method. Second, it is our intention to avoid tumour cell spread by use of a 'no-touch technique', because tumour cell spread is likely to occur with the commonly used technique of close dissection near the centrally located carcinoma. In conventional bile duct resection even in combination with partial or total liver resection this 'no-touch technique' is not feasible. As nobody would sample lymph nodes near a colorectal carcinoma or take a biopsy of such a tumour, these new methods follow more closely the principles of oncological surgery.

The results achieved so far do not allow any real conclusion. Some of our patients had lymph node metastasis undetected before and during operation. Other patients suffered from complications after surgery especially at the pancreatic anastomosis. We think that an evaluation for 5 years of at least 20 patients without surgical complications, and with bile duct tumours confined to the liver hilum without lymph node metastasis, is necessary to answer this question.

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1 Neuhaus P, Blumhardt G. Extended bile duct resection – a new oncological approach to the treatment of central bile duct carcinomas? *Langenbecks Arch Chir* 1994; 379: 123–8.
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Author's reply

Sir

Dr Neuhaus reminds us that his group has previously reported a surgical technique and concept similar to ours which appeared in *Langenbecks Archiv fur Chirurgie* in 1994. We did not mention this article because our manuscript was prepared before it was published. Since our own article was published, two more patients have undergone the same procedure. In an attempt to increase the chance of cure, our patients additionally underwent upper abdominal radiotherapy after operation.

We were pleased to find that we had come to the same concept and conclusions as Dr Neuhaus' distinguished group. Indeed, both articles carried identical messages for patients with hilar bile duct carcinoma: (1) combined liver transplantation and pancreatoduodenectomy seems rational in the quest for increased surgical radicality; (2) in addition to removal of the entire biliary tract and surrounding tissue, this approach reduces tumour cell spread as the hepatoduodenal ligament remains undissected ('no-touch' technique); (3) the procedure is well tolerated and leads to fewer nutritional consequences than upper abdominal exenteration ('cluster operation'). We fully agree that a larger cohort of patients with longer follow-up is required to assess oncological benefit.

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Randomized controlled multicentre study of the prevention of complications by octreotide in patients undergoing surgery for chronic pancreatitis

Sir

The article by Dr Friess and co-workers (*Br J Surg* 1995; 82: 1270–3) shows a significant decrease of pancreatic fistula and fluid collection in patients undergoing operation for chronic pancreatitis with octreotide treatment. Although pancreatic fistulas usually carry a substantial mortality and morbidity rate, in this study neither the mortality rate nor the length of the hospital stay was adversely affected, which suggests that the severity of the pancreatic fistula was minor.

By contrast, the number of complications other than pancreatic fistula and fluid collection was significantly increased in octreotide-treated patients ($n = 29$ *versus* $n = 16$; $P = 0{\cdot}0318$, Fisher's exact test). Patients treated with octreotide had significantly more severe systemic complications, such as pulmonary insufficiency, shock, sepsis, renal insufficiency and bleeding ($n = 21$ *versus* $n = 10$; $P = 0{\cdot}0346$). The authors explain these findings as a result of the lack of homogeneity between the two groups, although they have clearly stated that the groups were similar, specifically with respect to preoperative morbidity. They have therefore failed to demonstrate conclusively that these severe complications were not associated with the octreotide treatment

In summary, the data presented do not show a beneficial effect of octreotide regarding mortality rate and length of hospital stay. To the contrary, octreotide might precipitate serious systemic complications in these patients. As a result one would have to advocate extreme caution in the use of octreotide in patients with chronic pancreatitis and potentially other patients undergoing pancreatic surgery.

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Authors' reply

Sir

We appreciate the comments raised by Dr Frick regarding our trial. However, he has made several incorrect assumptions, which include discussing two hypotheses which he himself postulated retrospectively.

First, we would like to point out that Dr Frick made a minor error in counting: the number of complications other than pancreatic fistula and fluid collection is actually 31 (octreotide) *versus* 16 (placebo). Furthermore, he counted complications not patients. From *Table 2* of our paper it can be seen that 20 patients in the octreotide group had a total of 47 complications, whereas 37 patients in the placebo group had a total of 56 complications. Correct statistics should be based on patients, not on complications which counted the same patient up to seven times in this study. The number of patients with systemic complications (death, pulmonary insufficiency, shock, sepsis, renal insufficiency, bleeding) was 12 (octreotide) *versus* nine (placebo). These numbers are far from significant. Furthermore, the number of patients with complications other than pancreatic fistula or fluid collection is seven (octreotide) *versus* five (placebo).

Second, we would like to display a table which was eliminated from the original version of our manuscript because of lack of space, and which shows the distribution of patients with postoperative complications in the octreotide and placebo groups (*Table 1*).

Table 1

No. of patients	Octreotide ($n = 122$)	Placebo ($n = 125$)	Total ($n = 247$)
Without complications	102	88	190
With one complication	9	19	28
With two complications	4	16	20
With three complications	4	1	5
With four or more complications	1	0	1
No. of deaths	2	1	3

Third, including our study, four randomized placebo-controlled multicentre trials have independently proved that octreotide treatment given during operation reduces postoperative complications[1–3]. In all four trials the rate of postoperative complications was reduced by 50–65 per cent in patients treated with octreotide compared with patients receiving placebo. No severe side-effects of octreotide – such as those hypothesized by Dr Frick – were reported in any of these studies.

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1 Buchler MW, Friess H, Klempa I *et al* Role of octreotide in the prevention of postoperative complications following pancreatic resection. *Am J Surg* 1992; 163. 125–31.

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Impact of fine-needle aspiration cytology, ultrasonography and mammography on open biopsy rate in patients with benign breast disease

Sir

We read with interest the recent paper by Mr Green and colleagues concerning the reduction in open breast biopsy rates following the introduction of a diagnostic fine-needle aspiration cytology (FNAC) service (*Br J Surg* 1995; 82: 1509–11). In a similar study performed recently in our own unit, we have also observed a comparable trend towards the conservative management of breast disease thought to be benign on the basis of 'triple assessment' including FNAC. Sixty-four per cent of 174 patients referred to a symptomatic breast clinic over an 18-month period were managed by reassurance alone after such assessment, with no cases of 'missed cancer' presenting in the following 2-year follow-up period.

As in the study of Green *et al.*, we also found that open biopsy is still necessary for formal diagnosis in an important proportion of patients (17 *versus* 23 per cent) despite the use of preoperative FNAC. This requirement was due partly to patient preference for open biopsy despite benign assessment in a number of patients, but also to the (inevitable) inadequacy rate of FNAC (30 *versus* 22 per cent for Green *et al.*). When inadequate aspirates are taken into account, as recommended in the Quality Assurance Guidelines for Cytology reporting in the National Health Service Breast Screening Project[1], the sensitivity and specificity rates of FNAC are considerably lower than the figures quoted by Green *et al.*, and this may limit its usefulness in reassuring patients of the presence of benign disease. It has also been noted that while repeat FNAC after an initially inadequate aspirate often yields no additional diagnostic information, needle-core biopsy is often diagnostic[2]. It was interesting, therefore, to note that core biopsy was rarely used by Green and colleagues in the 'FNAC era' perhaps its increased use after initially unsatisfactory FNAC may allow further reduction in open biopsy rates for benign disease than reliance on imaging and FNAC alone.

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1 *Guidelines for Cytology Procedures and Reporting in Breast Cancer Screening* NHSBSP Publication Number 22, Trent RHA, Sheffield, UK.

2 Carty NJ, Ravichandran D, Carter C, Mudan S, Royle GT, Taylor I. Randomized comparison of fine-needle aspiration cytology and Biopty-Cut needle biopsy after unsatisfactory initial cytology of discrete breast lesions. *Br J Surg* 1994; 81: 1313–14.

Quality of life assessment in patients undergoing treatment for oesophageal carcinoma

Sir

I read with interest the recent article by Mr O'Hanlon and colleagues (*Br J Surg* 1995; 82: 1682–5). Their quality-of-life assessment in patients with oesophageal carcinoma again emphasizes the limitations of currently available treatments. The purpose of my communication is briefly to illustrate the potential of non-steroidal anti-inflammatory drugs (NSAIDS) in the chemoprevention and treatment of oesophageal carcinoma.

I agree with Mr O'Hanlon and co-workers that the natural history and treatment of oesophageal carcinoma does relate to patient quality-of-life. Consider the natural history of oesophageal carcinoma as a function of 'classic' risk factors such as alcohol intake, smoking and dietary deficiencies. These factors can contribute to the formation of precancerous lesions such as chronic oesophagitis and Barrett's oesophagus. Proinflammatory prostaglandin (PG) E_2 is implicated in oesophageal carcinogenesis as it appears to increase mucosal blood supply and rate of cell turnover[1] NSAIDs inhibit PGE_2 synthesis and could therefore help to prevent oesophageal carcinoma[2]

With respect to treatment, NSAIDs appear to have specific immunostimulatory or tumoricidal properties in the oesophagus[3].

NSAIDs *per se* may therefore be useful in the treatment of oesophageal carcinoma. NSAIDs may also help to reduce the side-effects of radiotherapy and surgery. Radiotherapy is dose-limited by the inflammatory side-effect of radiation oesophagitis, but NSAIDs could reverse this side-effect by inhibiting proinflammatory PGE_2 synthesis[4] as well as exerting tumoricidal effects

With respect to operation, PGE_2 has potential as a diagnostic or prognostic biomarker as oesophageal carcinomas produce excessive quantities of PGE_2. In this context, PGE_2 appears to be immunosuppressive and NSAIDs could help to restore immunoreactivity in patients considered eligible for operation PGE_2 bioassay could also be useful to predict postoperative relapse. In the study by Zhou and Jiang[5], PGE_2 blood level in 67 patients with carcinoma was measured before and after operation. PGE_2 levels were compared with 22 postoperative control patients and 20 healthy volunteers. In the patients with oesophageal carcinoma PGE_2 levels were closely correlated with carcinoma staging Following carcinoma resection, PGE_2 blood levels increased for a mean of 5 (range 2–8) months before relapse or clinical diagnosis of metastases. The effect of NSAIDs, on these biochemical and clinical parameters remains to be addressed.

In conclusion, PGE_2 has a far-reaching potential as a diagnostic or prognostic marker in oesophageal carcinoma. The potential of NSAIDs in the chemoprevention and treatment of oesophageal carcinoma deserves clinical evaluation. For example, empirical therapy with aspirin may help patients both clinically and with quality-of-life measures This approach could be supported by the co-administration of a gastroprotective agent such as omeprazole to prevent NSAID gastrotoxicity.

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Primary soft tissue sarcoma of the extremities in adults

Sir

Dr Karakousis and colleagues (*Br J Surg* 1995; 82: 1208–12) stated that 'the majority of authors agree that local recurrence contributes little to the development of distant metastases and death, although this has been disputed'. Do Karakousis *et al* agree with the majority? I have previously stated that I agree that local recurrence contributes little to the development of distant metastases[1]. In brief, I believe that circulating sarcoma cells challenge the immune defences of each patient. Defence systems that can destroy tumour cells circulating from the primary tumour can just as reliably destroy sarcoma cells circulating from a local recurrence. Thus, locally recurrent sarcoma is no more likely to metastasize than the primary tumour. Karakousis and colleagues have called this hypothesis 'interesting'. Do they agree with it? If not, do they have an alternative explanation for the innocent behaviour of this once dreaded surgical complication?

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1 Evans RA. Soft tissue sarcoma: the enigma of local recurrence *J Surg Oncol* 1993; 53: 88–91.

Author's reply

Sir

I read Dr Evans's comments with interest. I agree with the majority that local recurrence does not appear to make a statistically significant contribution to the development of distant recurrence[1]. However, this situation applies mainly to the first local recurrence. Repeat uncontrolled local recurrence diminishes the survival of the patients, and in some cases, through progressive dedifferentiation of the tumour, it increases the risk of distant recurrence. Dr Evans's stated hypothesis is that the body's defence mechanisms can cope with a certain amount of circulating tumour cells, and if these defences were capable of preventing distant metastases before removal of the primary tumour, they should be able to do the same with the subsequent local recurrence up to the time the latter assumes the same size as the primary tumour. I believe there is merit in this hypothesis. The traditional alternative explanation is that if the primary tumour did not have the biological capacity to shed tumour cells in sufficient number into the circulation to establish distant metastases, the local recurrence which is composed of essentially similar cells should not have that capacity either. The truth probably lies in considering the relationship of the host and the tumour, as far as the outcome is concerned, and not the one apart from the other

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1 Karakousis C, Proimakis C, Velez A, Driscoll D Local recurrence in soft tissue sarcomas and survival. *Annual Cancer Symposium of the Society of Surgical Oncology*, Boston, Massachusetts, March 1995: P18.

Lateral subcutaneous sphincterotomy for treatment of anal fissure in children

Sir

The authors of this paper (*Br J Surg* 1995; 82: 1341–2) appear to endorse the use of an operation causing direct surgical damage to the internal sphincteric mechanism in children as superior to anal dilatation in relief of the symptoms of fissure *in ano*. The patients reviewed have not been subjected to any controlled trial, and they even record in their discussion that there are no comparative data regarding the complications of a simple anal dilatation in children. In particular, they note various long-term follow-ups of adult patients who have undergone anal dilatation but do not even record their own long-term follow-up of the operation that they advocate. As a full-time paediatric surgeon I, for one, will not be surgically dividing the internal sphincter in the children under my care with a simple fissure *in ano*.

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Authors' reply

Sir

Mr Turnock criticizes our study for not being a controlled trial and for failing to record the long-term follow-up of our patients. We believe that he has misunderstood the basis of our report which was purely an observational study of a procedure recognized to be effective in adult surgery. There is little point in embarking on a randomized controlled trial of two treatments unless sufficient numbers can be recruited so that any significant variation in outcome can be determined. Surgical treatment for fissure *in ano* in children is relatively rare (in our hospital 23 children required such surgery over a 54-month period) and sufficient numbers for a randomized trial may well be impossible to obtain in a single hospital

It is difficult to quote our long-term results when the last patient underwent surgery only 16 months ago Our patients are, however, still under review and to date there are no recurrences or indication of faecal incontinence.

Finally, Mr Turnock criticizes us for failing to provide comparative data on anal dilatation in children. During our literature researches we were unable to find any publication of any data relating to children who had undergone that procedure. Furthermore, none of the three references of this procedure in children quoted in our paper were supported by published data. The potential consequences of the operation advocated by Mr Turnock may not become apparent for many years. Until we can be furnished with evidence to the contrary we will continue to advise a procedure that divides rather than disrupts the internal anal sphincter

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Ambulatory oesophageal bile reflux monitoring in Barrett's oesophagus

Sir

We were interested to read the article by Mr Caldwell and colleagues (*Br J Surg* 1995; 82. 657–60). We agree that although there has been some concern recently about the relevance of the original validation studies as well as doubts over how seriously any quantitative data can be interpreted[1,2], the Bilitec 2000 (Synectics, Stockholm, Sweden) bile probe may well prove to be a useful tool in identifying pathological duodenogastro-oesophageal reflux in the clinical setting. However, several unanswered questions are raised by the article.

It is not clear in the method whether all the patients had stopped acid suppression treatment, although this is assumed. It would also have been interesting to see the results for oesophageal acid exposure which were missing from *Table 1* Could it be that the group of normal controls is in fact a group of latent refluxers? This possibility may explain why, in this group, there is such a high reading for bilirubin absorbance in the postprandial period. Surely this period is extremely interesting in terms of possible bile reflux, as it is in acid reflux, and should not be excluded. Other studies have included the entire 24 h in the analysis[2–5] and have shown that in normal controls the usual finding is a percentage time for absorbance more than 0·15 or less than 1 per cent The authors state that 'analysis was confined to the fasting supine period and the interdigestive period because a bench study had found that many common foodstuffs had absorbance values similar to that of bilirubin, and that by excluding the postprandial period this artefact was minimized'. This seems to be doing the wrong thing for the wrong reason· in the normal controls there should be only minimal postprandial reflux, and so foodstuffs should rarely come into contact with the bile probe (and only transiently when the patient swallows). Surely the authors should be modifying the diet to avoid dark-coloured food and not excluding important time periods in their analysis.

The article also states that patients were asked to avoid food, tea and coffee between meals and to avoid eating for 2 h before retiring to bed. However this advice would seem to be unphysiological as it breaks from the patients' normal 24-h schedule and detracts therefore from the essence of ambulatory monitoring. Most other groups using the Bilitec 2000 system simply ask patients to avoid foods of a dark colour which may coincide with bilirubin absorbance[2–6]

Certainly more work needs to be done in establishing normal values for the Bilitec 2000 bile probe before more accurate interpretation of the results can be made. It does, however, look to be a promising adjunct to pH monitoring in the understanding of gastro-oesophageal reflux disease.

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Authors' reply

Sir

We thank Messrs Marshall and Anggiansah for their interest in our study All patients had discontinued acid suppression medication 10 days before investigation The data on acid exposure are recorded in Results as the mean(s.e.m.) DeMeester acid score which, for the control group, was given as 6·8(1·3) This value excludes the possibility of this group being latent refluxers.

While we agree that the postprandial period is of great interest, the presence of a gap at the tip of the probe has proved on a number of occasions to compromise recordings, not just because of the colour of the food but because food particles may become trapped for variable periods at this point, thus distorting the results.

Again the instructions given to the patients about intake between meals were aimed at standardizing their intake of coloured substances. Opinion is divided on whether it is more physiological to give a colour-free diet or to exclude coloured foodstuffs between meals. In an outpatient setting, patient compliance is less of a problem when normal diet is permitted for most of the period.

Bile monitoring technology is in its infancy, and the limitations of current techniques must be recognized and addressed. The publication of studies on large series of normal volunteers is awaited, and fixed protocols for bile monitoring are yet to be established.

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Bladder injury during laparoscopic abdominoperineal resection

Sir

The article by Mr Williams and colleagues (*Br J Surg* 1995; 82: 1207) illustrates the danger of rectal resection by 'faith and not by sight'. Laparoscopic surgery is not difficult in the pelvis, and a good technique will enable rectal dissection to be simpler than at open operation. We have performed laparoscopic abdominal–perineal resection in nine patients, with a median operating time of 120 (range 65–185) min without any intraoperative morbidity. None of these patients required abdominal incision other than port and stoma sites. Laparoscopic as well as conventional open surgery must be performed with a good understanding of normal and possible variant anatomy, and all operations must be performed only under good vision and in the correct planes. Careless surgery without regard for anatomical boundaries can only mean poor results.

An open abdominal approach is not needed to reach the correct plane for perineal dissection. Once the pelvic floor muscles are reached, the anococcygeal ligaments are incised anterior to the tip of the coccyx. This manoeuvre will bring us to the presacral plane just posterior to the rectum. The plane can be developed further after the levator ani are divided as far laterally as possible next to the pelvic side wall. Waldeyer's and Denonvilliers' fascia should have been divided laparoscopically, otherwise these can be easily visualized and divided from below. Successful surgery depends on a good knowledge of anatomy and good visualization of the different planes. If this principle is not followed, the surgical literature will soon be swarming with reports of all sorts of possible complications because of dissection in the wrong planes

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Author's reply

Sir

We thank Mr Seow-Choen and colleagues for their interest in our paper and would agree wholeheartedly with their comments about the need for good knowledge and visualization of the planes in the pelvis It appears to us that the experience of most units in this particular operation is rather small. It would be interesting to see how the morbidity rates compare with those of the conventional approach, as experienced by centres increasing beyond the small numbers currently available for review.

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Experimental study to show that growth hormone treatment before trauma increases glutamine uptake in the intestinal tract

Sir

We read with interest the paper from Dr Mjaaland and colleagues (*Br J Surg* 1995; 82: 1076–9) investigating the effect of growth hormone treatment on glutamine flux after operative trauma. Operative stress causes an increased release of glutamine from skeletal muscle, with an increased intestinal uptake of glutamine[1,2]. This augmented intestinal glutamine metabolism is mediated by both glucagon[3] and glucocorticoids[4] and is thought to be necessary to support intestinal energy and nitrogen requirements at a time when food intake is temporarily interrupted[2]. An insufficient luminal or vascular supply of glutamine to the intestinal tract may result in ultrastructural intestinal changes and failure of the gut mucosal barrier[5]. These suggestions have led to the development of therapeutic strategies with the twin aims of preserving skeletal muscle mass and maintaining intestinal function in traumatized patients.

Administration of nutrition by the enteral route or of selective intestinal nutrients (glutamine, short-chain fatty acids), growth factors and gut hormones have all been proposed as methods of improving intestinal function during critical illness[6], whereas glutamine, ornithine-alpha-ketoglutarate or branched-chain amino acids have been investigated as means of reducing proteolysis of skeletal muscle[7]

Exogenous supply of glutamine (or of ornithine-alpha-ketoglutarate) after operation meets the increased intestinal consumption of circulating glutamine and prevents skeletal muscle breakdown[7]. In their study on experimental operative trauma, Dr Mjaaland and colleagues have now shown that not only does treatment with growth hormone reduce skeletal muscle release of glutamine but it also increases intestinal glutamine uptake. While these therapies are theoretically attractive, it remains to be demonstrated whether administration of supplemental glutamine or growth hormone will improve outcome in patients after surgery or major trauma.

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Early parietal recurrence of adenocarcinoma of the colon after laparoscopic colectomy

Port site metastasis after laparoscopic colorectal surgery for cure of malignancy

Sir

I read with interest the case report by Dr Montorsi and co-workers (*Br J Surg* 1995; 82: 1036–7) as well as the earlier report by Drs Wexner and Cohen (*Br J Surg* 1995; 82: 295–8) and the correspondence that ensued.

There is no doubt that the concerns expressed are justified insofar as we have yet to explain why tumour seeding occurs. Nevertheless, implantation of malignant cells in surgical wounds is well described and particularly notorious in gallbladder cancer, and it seems logical that the tumour cells must have originated by spillage within the abdominal cavity rather than by blood-borne spread. While attempts have been made to minimize such spillage and contamination of the wound by technical methods including specimen bag retrieval, very few reports describe the instrumentation that was used to handle the tumour. Virtually all the instrumentation available on the market, and certainly the older instrumentation, is traumatic and crushes the serosa of the colon to some degree or another as compared with the more traditional technique in which the surgeon tends to use his fingers.

It is this mechanical trauma that must result in the spillage of tumour cells, and it is likely that these implant at sites of surgical trauma or crush injury, which can take place where a stiff port has been applied to the abdominal wall for any length of time. The latter may explain why port puncture technique may be a factor.

For this reason, in my own personal experience of 37 laparoscopically assisted colonic resections for malignant disease, I have studiously avoided crushing instruments in handling the bowel anywhere near the primary tumour, as yet there has not been a single port site recurrence. In addition the port sites have been irrigated with aqueous Betadine (Napp Laboratories, Cambridge, UK) in full concentration before closure.

The physiological benefits of laparoscopically assisted colectomy seem to be retained despite the size of the subsequent incision to complete the procedure, and we therefore should not be obsessed with attempting minimal incisions or totally closed procedures until we have learnt more about the technology.

It is vital that what is potentially a very valuable addition to the surgical armamentarium should not be discredited or abandoned without a fair hearing.

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Pain relief after inguinal hernia repair: a randomized double-blind study

Sir

We read with interest the paper by Mr Nehra and colleagues (*Br J Surg* 1995; 82: 1245–7) in which they state that bupivacaine ilioinguinal nerve block alone provided good immediate pain relief after operation, but the addition of aspirin–papaveretum combination was necessary to provide the best results for longer postoperative analgesia. Our experience is somewhat at variance with their findings. We randomly allocated 75 patients undergoing inguinal herniorrhaphy under general anaesthesia, to either no pre-emptive analgesia or wound infiltration or ilioinguinal field block using 20 ml 0·5 per cent bupivacaine before the incision. A standard anaesthetic technique was used, and the repair carried out using a modified Bassini repair by the same surgeon. Pain was assessed by an independent observer twice daily using a standard linear analogue scale. We found no significant difference (Mann–Whitney *U* test) in severity of pain as measured by linear analogue pain scores (*Table 1*). Furthermore, mean pethidine requirements over the first 24 h were similar in the three groups

Table 1 Linear analogue pain score (mm)

		No intraoperative analgesia	Ilioinguinal block	Bupivacaine infiltration
Day 1	a.m.	28 (1–94)	31 (2–91)	25 (1–93)
	p.m.	19 (0–79)	32 (1–94)	23 (2–71)
Day 2	a.m.	14 (1–79)	19 (1–60)	15 (1–78)

Values expressed are median (range)

Other authors have shown subcutaneous bupivacaine to be ineffective after inguinal herniorrhaphy[1]. More importantly, in our experience, the use of either an ilioinguinal nerve block or wound infiltration before incision was not by itself associated with either a significantly longer initial pain-free period after operation or a significant reduction in postoperative pain at 24 h. It may be that this was because intraoperative fentanyl (Sublimaze; Janssen Pharmaceuticals, Buckinghamshire, UK) and ketorolac (Toradol; Syntex Pharmaceuticals, Berkshire, UK) were part of the anaesthetic technique and would themselves have influenced pain relief and added to any pre-emptive effects. None the less, we do agree with Nehra *et al.* that additional analgesia is required to enable the postoperative pain-free period to extend beyond the first 24 h. Since completion of our study, we have changed over to the Lichtenstein technique for inguinal hernia repair because we believe it to be better tolerated by patients undergoing day-case surgery, and we do add diclofenac 100 mg per rectum at the end of the procedure to extend the postoperative pain-free period.

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Total mesorectal excision is optimal surgery for rectal cancer: a Scandinavian consensus

Sir

We refer to the Leading Article by Mr Heald (*Br J Surg* 1995: 82. 1297–9), which stresses the great variability in the results of treating rectal cancer between centres and the need to establish that such differences are 'real' Attention is also drawn to the work of Quirke and colleagues on assessing the importance of circumferential resection margin (CRM) involvement by tumour.

To date, the incidence of CRM involvement in published series has varied between 6·5 per cent[1] and 36 per cent[2] Some of the variation in findings is presumably surgeon-related and some due to the difference in protocols used in assessing the surgical specimens. It is our view that the definition of the CRM (also at times referred to as the lateral resection margin), used by some authors[2,3] to refer to a zone of tissue 1 mm in width around the circumference of the specimen, differs from the usual meaning of a resection margin and could also account for some of the differences between series. To most pathologists and surgeons a resection margin is literally the line along which the scalpel or diathermy point has passed when tissue is excised. As Quirke *et al.*[4] have indicated, circumferential clearance in rectal cancer is often very limited It follows that some cases will be found to have invaded the 1 mm marginal zone yet not have involved a line of resection. These patients retain the possibility of being cured of their tumour, assuming there are no known distant metastases. We have found from survival studies in colorectal cancer that when tumour is present in a line of resection, there is justification for classifying the case as clinicopathological stage D (i.e. known residual tumour)[5]. In this study we demonstrated tumour in a circumferential line of resection in 54 of 706 consecutive patients with rectal cancer (7 6 per cent). This figure is similar to the incidence of 6 5 per cent recorded by Cawthorne *et al*[1] for CRM involvement. As these authors did not define their resection margin as having thickness and their patients had a very poor survival, it seems likely that they were also referring to a line of resection. In comparing the results of these two series, it is noteworthy that in both the patients were from only one institution, the method of specimen dissection was similar and only one pathologist was involved.

To avoid confusion in the future, we would advocate use of the term circumferential marginal zone (CMZ), preceded by a statement of the width, in order to make a clear distinction from the terms 'resection margin' and 'line of surgical resection' which we regard as synonymous. It would be informative if authors were to record data on both the involvement of the CMZ as well as the circumferential line of resection

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1 Cawthorne SJ, Parums DV, Gibbs NM *et al* Extent of mesorectal spread and involvement of lateral resection margin as prognostic factors after surgery for rectal cancer. *Lancet* 1990, 335: 1055–9.
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Prospective evaluation of ultrasonography and liver function tests for preoperative assessment of the bile duct

Sir

I read with interest the study by Mr Welbourn and colleagues (*Br J Surg* 1995; 82· 1371–3). Data on the predictive value of diagnostic parameters are most informative when correlated with disease prevalence, hence the utility of correlating bile duct diameter with age, as in *Fig 1* of this study, which takes cognisance of the age-related nature of choledocholithiasis[1]. Likewise, the prevalence of biochemical markers of biliary obstruction should have been correlated with age, because even subtle biochemical derangements have a greater predictive value for choledocholithiasis in the old than the young, due to the positive correlation between positive predictive value and disease prevalence[2] Similarly, the negative predictive value of both biochemical and ultrasonographic stigmata exponentially decreases with advancing age to a point at which even a perfectly normal hepatic biochemical profile and/or bile duct diameter may fail to rule out coexisting choledocholithiasis. Clinical evaluation may fill the vital 'information gap', when both biochemical and ultrasonographic stigmata lack sufficient predictive value to confirm or refute the diagnosis of choledocholithiasis. Thus all clinicians must be prepared to follow their instincts when such dilemmas occur in the course of management of elderly patients

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Percutaneous cholecystostomy: a valuable technique in high-risk patients with presumed acute cholecystitis

Sir

In the acute phase of cholecystitis I agree with the procedure described in the paper by Mr Melin and colleagues (*Br J Surg* 1995; 82· 1274–7). I feel, however, that the following are worth emphasizing:

(1) The diagnosis of acute cholecystitis can be established by clinical and laboratory findings and ultrasonography; computed tomography or cholescintigraphy is not necessary.
(2) Transhepatic placement of the drainage should always be the aim, the transperitoneal route should happen only accidentally.
(3) Percutaneous cholecystostomy can be achieved much more easily and faster by ultrasonographic guidance than by computed tomography.
(4) Radiological checking should be performed immediately after placement (and not 24 h later) by fistulography with cholecystography and possibly cholangiography to detect and correct possible catheter dislodgement or extravasation. Furthermore diagnostic radiography of the gallbladder and ducts may also be helpful at this very early stage.
(5) If clinical symptoms fail to improve within 24 h of cholecystostomy, a change in therapy should be considered, perhaps even operation. To wait longer (even 2 days) is dangerous, especially if the content of the gallbladder is not purulent. In these cases one must consider that the incidence of gangrene of the gallbladder is very high.

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British Journal of Surgery 1996, 83, 429

Book reviews

The Fellowship Short-Answer Paper

F. G. Smiddy (ed.). 215 × 138 mm. Pp. 365. Not illustrated. 1995. Oxford: Blackwell Science. £18·95.

The short answer paper in the Clinical Surgery in General examination of the Royal College of Surgeons comprises eight questions to be answered in 2 h. Candidates are required to confine each answer to two pages of the answer book. These constraints demand a special technique of answering and also an understanding of the way in which the paper is marked, yet few candidates will have had much recent practice in writing examination answers, and only a minority seem to receive any guidance on how to approach the paper.

This book sets out 136 typical short answer questions but falls short in the guidance it offers to candidates on answering them Candidates need to be told about the limitations of space and time, and that the questions are marked from a crib listing the scoring points, some of which may be defined as essential. They need advice on the extent to which note form and lists are acceptable, and on layout. Not only is this information lacking from the book, but the specimen answers provided are misleading. All are longer than could be accommodated in the answer book and the scoring points are not highlighted. Many can be criticized for vagueness, irrelevance, undue emphasis on a particular piece of research, poor organization or archaic views. Fellowship candidates will find little help from this volume.

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Atlas of Surgical Oncology

K. I. Bland, C. P. Karakousis and E. M. Copeland III (eds). 283 × 218 mm. Pp 810. Illustrated. 1995. Philadelphia, Pennsylvania: W. B. Saunders. £107.

The preface of this book states that the purpose is to provide a readable, comprehensive text depicting the rationale for and illustrating basic operative principles essential to the therapy of various benign and malignant solid tumours. In the main I think it succeeds. It is a multiauthor text written in a style which would be more familiar to North American surgeons than those from the UK. It begins with a chapter outlining the principles of oncological surgery and the assessment of operative risk, which contains exhaustive tables and algorithms of care. It then goes on to deal with, in turn, tumours of various organs, beginning with the skin, moving to the thyroid, parathyroid, salivary gland, etc. I found these individually variable. The chapters on the treatment of cutaneous melanoma, breast cancer and reconstruction, and urological neoplasms were particularly well presented. I did, however, find a number of deficiencies. Osteosarcoma of long bones and the reconstruction thereof was not covered at all and there was little detail concerning total gastrectomy, the treatment of hilar tumours and biliary bypass. The North American bias was clearly seen in the detailed description of anastomotic techniques using staplers, with little on hand-sewn anastomosis particularly of the colon and rectum.

Overall the book is well illustrated as one might expect with an atlas. In the UK there are few surgeons who regard themselves as surgical oncologists, but many who undertake oncological procedures. This book collects together many aspects of the surgery of cancer and, therefore, I think it does have a place. I regard it as more of a reference volume for dealing with the things we see infrequently and it will, as time goes by, require revision to keep up to date.

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Atlas of Cardiothoracic Surgery

D. C. Sabiston Jr (ed.). 285 × 220 mm. Pp. 598. Illustrated 1995. Philadelphia, Pennsylvania: W. B Saunders. £121.

Although several atlas-style books have been published in the field of cardiothoracic surgery, this new volume offers significant advantages over its predecessors. First, it is comprehensive, covering in depth both cardiac and thoracic procedures. This combination is interesting as the origin of the book is the USA, where cardiac and vascular rather than cardiac and thoracic has often been the mixture of choice. The cardiothoracic content will be of immediate appeal to trainees and established surgeons in the UK. Second, it is commendably up to date. Newer techniques such as thoracoscopic procedures and the Maze procedure for atrial arrythmias are good examples Third, it is a quality publication Some previous atlas-style books have prioritized colour pictures at the expense of textual information. This volume reverts to plain old black and white artwork which is, nevertheless, easy to understand and admirably executed. The accompanying text from a wide group of contributors is concise but accurate. Knowing the editor, Dr David Sabiston from Duke University, the quality of the book comes as no surprise This new atlas, combining cardiac and thoracic surgical procedures, sets a new standard. Although not inexpensive, it would be a good investment either for the cardiothoracic trainee or for the departmental library

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British Journal of Surgery 1996, 83, 430

Notices and announcements

15–16 March 1996
Advance Minimal Access Surgery for Theatre Personnel
Liverpool, UK
Information: J. O'Leary, Training Manager, MASTER Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

28–29 March 1996
Measurements in Wound Healing
Southampton, UK
Information: G. Kennedy, IPSM Meetings and Exhibitions, 4 Campleshon Road, York YO2 1PE, UK

31 March–3 April 1996
Trauma and Critical Care – 1996
Las Vegas, Nevada, USA
Information: Carol Williams, Trauma Department, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611, USA

1–2 April 1996
Injury Research Group Annual Meeting
Manchester, UK
Information: Dr R. N. Barton, North Western Injury Research Centre, Stopford Building, Oxford Road, Manchester M13 9PT, UK

1–2 April 1996
Congres Francophone de Coelio-Chirurgie
Deauville, France
Information: J. P. COM, CID BP 171, F14800 Deauville, France

3–5 April 1996
1st World Conference on the Prevention and Treatment of Caustic Oesophageal Burns in Children
Izmir, Turkey
Information: Professor O. Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, TR-35100 Izmir, Turkey

6–8 April 1996
7th Annual Scientific Conference — Current Concepts in Thyroid Disease
Doha, Qatar
Information: Dr A A. Gahani, P.O Box 3050, Doha, Qatar

10–12 April 1996
96th Annual Congress of the Japan Surgical Society
Chiba, Japan
Information. K Isono, Department of Surgery II, Chiba University School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260, Japan

11–12 April 1996
Endovascular Aortic Aneurysm Surgery
Nottingham, UK
Information. B. R. Hopkinson, Consultant Surgeon, University Hospital, Nottingham NG7 2UH, UK

14–17 April 1996
American College of Surgeons 24th Annual Spring Meeting
New York, USA
Information: Ms N. Sutton, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611, USA

14–18 April 1996
26th Biennial Congress of the International Society of University Colon and Rectal Surgeons
Lisbon, Portugal
Information: TOP Tours, Congress Department, R. Luciano Cordeiro, 116–1050 Lisboa, Portugal

18–19 April 1996
Femoro-Distal Workshop
Bath, UK
Information: Mrs K Cox, Secretary to Professor M. Horrocks, Department of Surgery, Royal United Hospital, Bath BA1 3NG, UK

22–23 April 1996
International Hernia Conference 1996
London, UK
Information: C. Cook or C. Fowler, SPA, 3 Bedfordbury, Covent Garden, London WC2N 4BP, UK

5–9 May 1996
1st Congress of the World Association for Laser Therapy 'WALT'
Jerusalem, Israel
Information. World Association for LASER Therapy, c/o PO Box 50006, Tel Aviv 61500, Israel

7–10 May 1996
Research Methods in Surgery
London, UK
Information. Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

12–15 May 1996
29th Annual Meeting of the Pacific Association of Pediatric Surgeons
Singapore
Information: Secretariat, Academy of Medicine, 16 College Road, Singapore 0316

15–18 May 1996
7th International Symposium on Pediatric Neuro-Oncology
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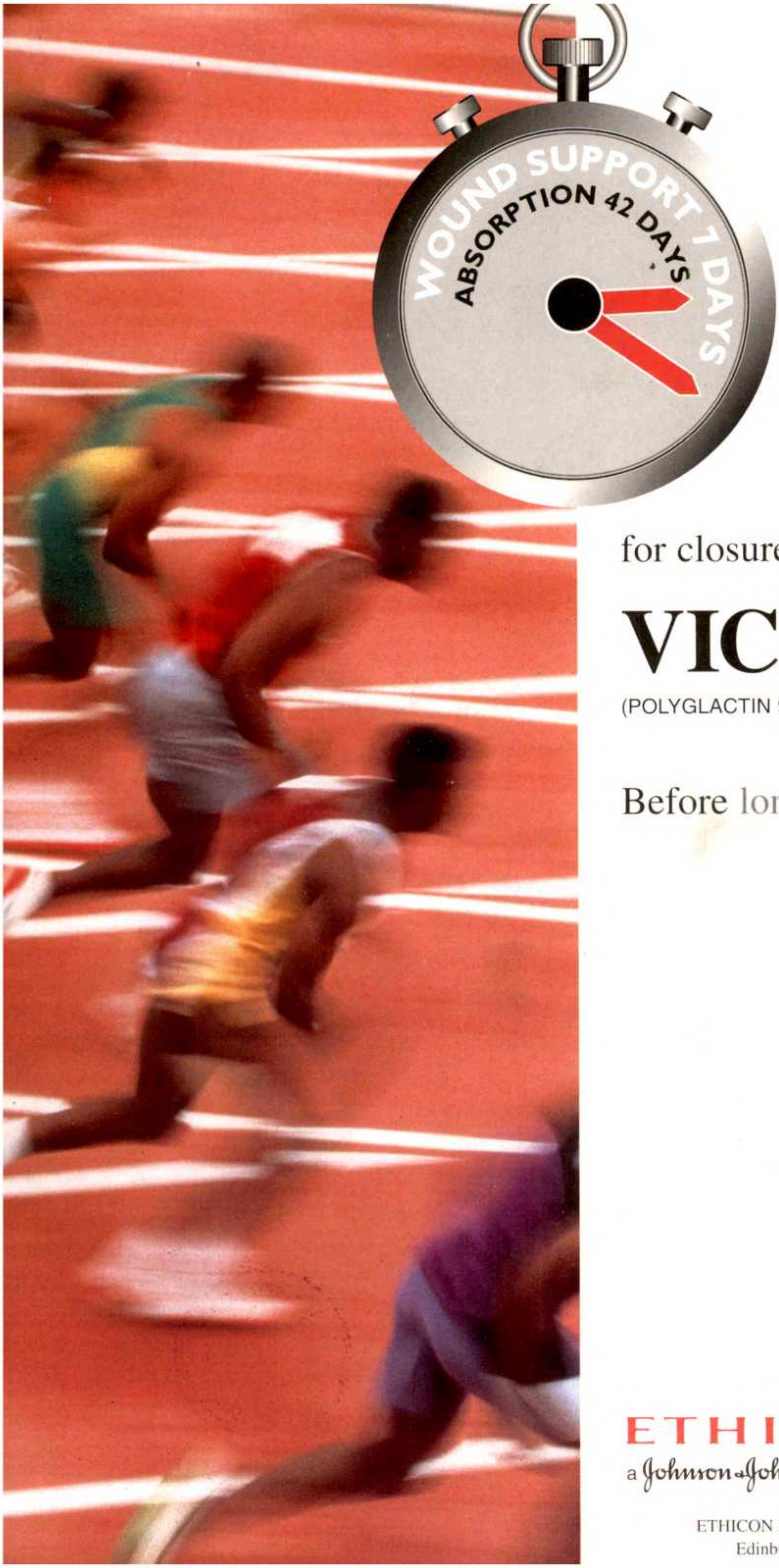

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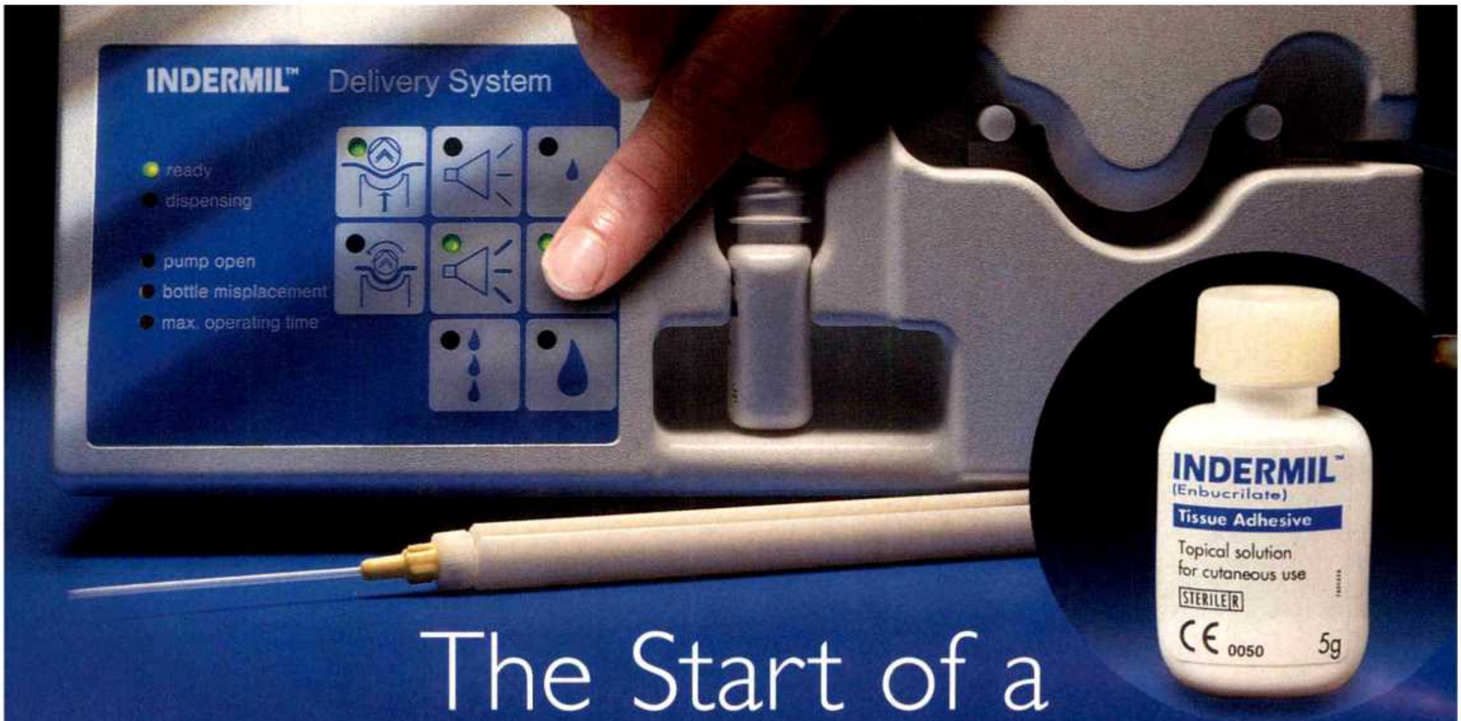

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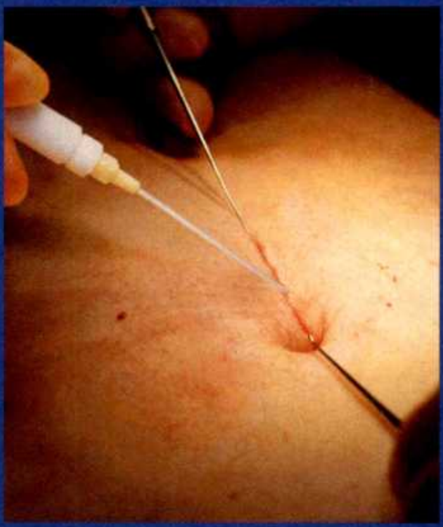

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Education. A major part of EDS activities will be the promotion of high-quality educational courses in all apsects of gastrointestinal surgical disease. Already three such courses have been organized dealing with standard treatment of pancreatic diseases (Madgeburg, December 1995), advances in pancreatic diseases (Athens, 1996) and gastro-oesophageal reflux disease (Berne, May 1996). A regular programme of educational courses is planned.

Research. Through the generous sponsorship of the pharmaceutical industry, EDS is able to offer up to ten research fellowships to pay the salary of promising young researchers active in surgical gastroenterology. These fellowships will be allocated on a competitive basis and it is hoped they will encourage high-quality collaborative work, and raise the profile of surgical gastroenterological research. Further details of these awards will be announced shortly.

First general meeting. A foundation meeting has already been held, and the founder members are listed below. The first annual meeting of EDS will take place in November 1996, during the United European Gastroenterology Week meeting in Paris. At that meeting an election will be held for officers and council members. The Society has established a transitional board to manage its affairs until the elected council can take over. Transitional board members are indicated on the list of founder members. Further information about EDS can be obtained from the founder members, and applications for membership should be made to European Digestive Surgery, c/o Karger AG, Allschwilerstrasse 10, PO Box, CH-4009 Basel, Switzerland.

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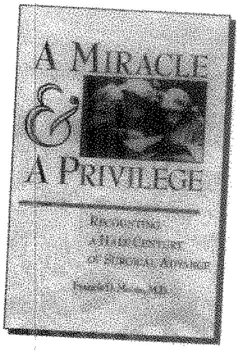

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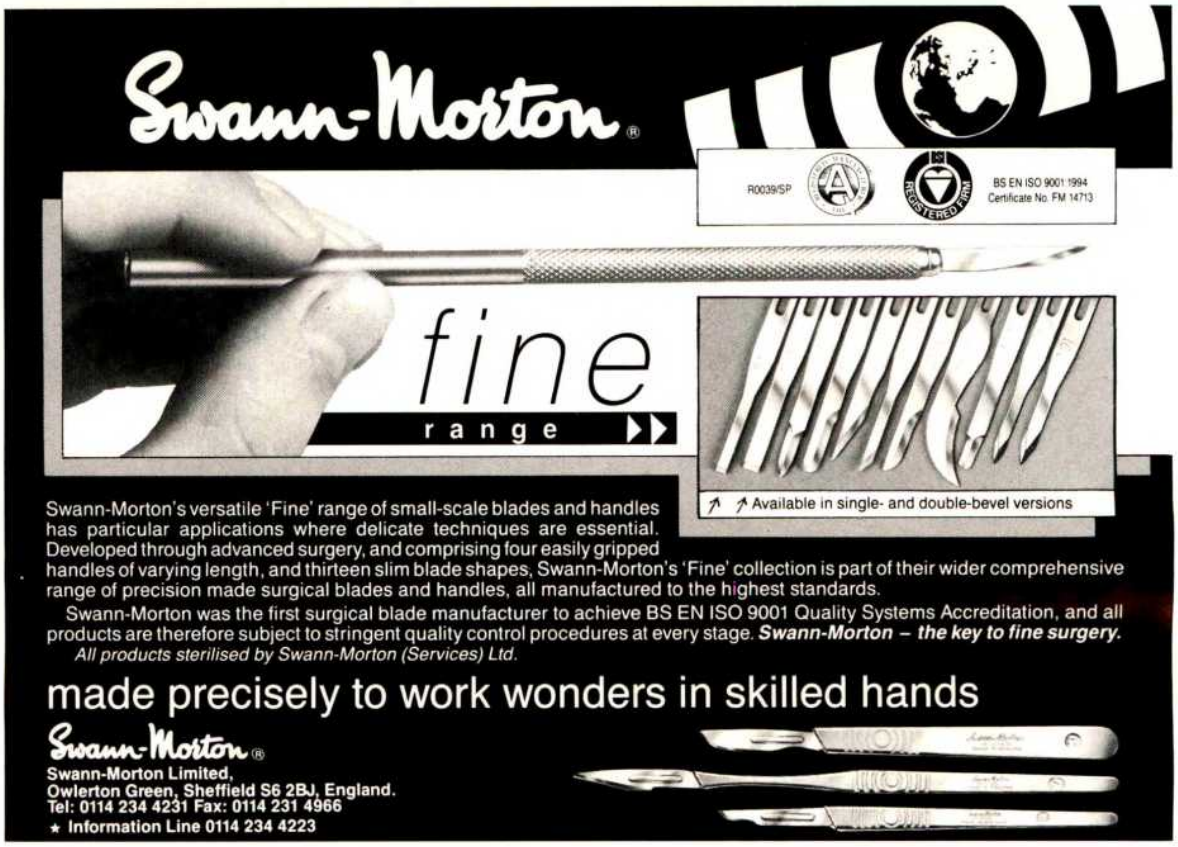

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Telepresence surgery

To date, applications of telemedicine have been limited to diagnostic imaging and remote clinical consultation. Operating on patients who are at locations distant from their surgeons has not, so far, been feasible. However, recent advances in electronics, telecommunications and robotics technologies, combined with knowledge gained from several decades of remote manipulation in hazardous industrial environments, have expedited the development of telepresence surgery for clinical practice.

The foundations of telepresence lie in the atomic energy industry, where methods were developed almost 40 years ago for the remote handling of dangerous isotopes[1]. Teleoperation, the manipulation of objects in remote locations by human operators who maintain direct and continuous control, allowed tasks to be performed safely by technicians who viewed the hazardous environments on television screens. Procedures such as moving large barrels of radioactive waste or assembling reactor components were controlled by operators using joysticks, similar to those of early arcade games. This level of control was adequate for tasks requiring only approximate positioning and of minimal complexity, but it did not provide the sensory cues needed for operators to use fine motor skills, such as those required in surgery.

Telepresence adds multisensory input from the remote environment to the human operator, using high-fidelity visual, audio and haptic (tactile) cues to create the perception that the operator is physically present at the remote location. In telepresence, emphasis is placed on developing a natural interface for the human operator. For example, a remotely located screwdriver tip can be crudely controlled by an operator manipulating levers (teleoperation), or it can be controlled by an operator holding an actual screwdriver handle, who can sense the torque applied as the screw is turned (telepresence)[2].

In telepresence surgery a procedure is performed on a patient physically remote from the surgeon, who operates from a console that provides an immersive sensory interface, thus creating the illusion for the surgeon of actual presence in the distant operating theatre. Telepresence is not virtual reality; in the latter the remote environment is created by computer software and is completely simulated. Nor does telepresence surgery involve robot-assisted operations, in which a robot responds to a preprogrammed sequence of instructions generated by a computer, as in automated laparoscope positioning. In telepresence surgery the surgeon manipulates real tissues at a remote location, to which he or she is linked only by electronics[3].

A prototype telepresence surgery system has been developed by Philip Green and colleagues at the Stanford Research Institute (SRI)[4]. The system consists of a surgeon's workstation and a remote surgical unit. The surgeon's workstation provides a colour, high-resolution, stereo (three-dimensional) image of the operative field, which can be magnified as desired. Beneath the imaging screen are conventional surgical instrument handles, which are grasped by the surgeon. The ergonomic design provides a completely natural orientation of the eye–hand axis normally present in the operating theatre. Stereophonic audio input enhances the surgeon's sense of presence at the remote site. The remote surgical unit is positioned over the operative field and has two high-resolution digital video cameras oriented to provide stereoscopic images for the surgeon. Beneath the cameras are servo-controlled manipulator arms, with interchangeable surgical instrument tips on the ends. Hand motions at the surgeon's workstation are translated precisely and immediately to the remote manipulator arms via a computer controller. To the surgeon, the instrument tips appear to be attached to the instrument handles, although they are connected only by an electronic cable.

The system provides tactile feedback to the surgeon, allowing characteristics of tissues at the remote location to be sensed by the surgeon's hands. For example, when grasping or retracting tissues, the surgeon instantly feels the sense of resistance to stretch. Thus, the operator can immediately and intuitively adjust tension to prevent tearing. Force feedback, true stereoscopic vision and natural eye–hand orientation all contribute to the sense of the surgeon being present in the remote environment[5].

Using the prototype telepresence system, common operative procedures have been carried out on live pigs, including cholecystectomy, nephrectomy, repair of arterial laceration, anastomosis of the small intestine, and closure of gastrotomy and enterotomy. Results have been comparable to those obtained using conventional techniques, establishing the feasibility of the new technology[6].

The obvious use of telepresence surgery is in extending the capabilities of surgeons to locations where specialist care is unavailable. For the military, battlefield casualties might receive definitive emergency surgery near the site of wounding. In the civilian setting, hands-on consultation and assistance might be provided to rural district hospitals. The remote location, however, need not be far away. Telepresence surgery could be used to treat casualties isolated from contaminated or hazardous environments, thus minimizing risks to the operating team. Another major application is likely in laparoscopic surgery, in which the manipulator arms could be introduced through 10–12-mm cannulas, allowing surgeons to regain the natural eye–hand orientation, fulcrum and tactile feedback lost in current systems. Telepresence technology can also be used to scale down a surgeon's hand motions; a 10-mm hand excursion can be scaled to 1 mm, or even 0·1 mm, at the tissue level and tremor can be dampened electronically. Force feedback can be scaled up, providing greater tactile sensation to the surgeon. The resulting enhancement of dexterity should extend the potential applications of telepresence to microscopic and endoscopic surgery.

Preclinical trials of a telepresence system for minimally invasive surgery have just begun at SRI; other groups, including those of Professor Gerhard Buess in Tübingen, Germany, and Drs Steve Charles and Ian Hunter in the USA, have telepresence instruments in development. By the end of the millennium, telepresence surgery may well be an integral component of national telemedicine systems and a fixture in modern operating theatres.

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British Journal of Surgery 1996, 83, 435–436

Thoracic outlet syndromes

The thoracic outlet syndromes (TOSs) are a group of common conditions caused by compression of the nerves and vessels supplying the upper limb[1]. Symptoms vary from mild to limb threatening and might be ignored by many physicians as they mimic common, but difficult to treat, conditions such as tension headache or fatigue syndromes. Clinical diagnosis, appropriate investigation and operation, reserved for carefully selected patients, yield satisfying and sometimes dramatic results. The prevalence of TOS is difficult to estimate, but in a 2-year period the authors evaluated 110 patients and operated on 35 from a population of 350000.

Arterial, venous and neurological features often coexist; treatment should be directed at the dominant component. Arterial TOS, often caused by bony costoclavicular compression or a cervical rib, is associated with aching, heaviness, fatigue, weakness and pallor due to brachial ischaemia. Late presentations include distal emboli or poststenotic aneurysm. Abduction, elbow flexion and external rotation of the upper limb in the coronal plane, with slow finger clenching for 3 min (Roos test), reproduces the symptoms, which occur when the patient works with the arm elevated. The radial pulse may be reduced or obliterated during this manoeuvre and an infraclavicular bruit may be heard. However, patients with severe neurological symptoms can be overlooked if the examiner focuses too closely on positional pulse changes. Radiographs may show bony anomalies. Duplex ultrasonography demonstrates velocity shifts and turbulence in the subclavian artery, and flow reduction or obliteration in the axillary artery. Arteriography has a high false positive rate and should be reserved for patients with arterial damage. In the authors' series, the Roos test was positive in 96 per cent of cases proven at operation and duplex scanning in 93 per cent; 62 per cent had a bruit and pulse reduction[2]. To date, 19 patients have had normal postoperative studies. Whatever the mechanism of arterial compression, the fulcrum is always the first rib, so transaxillary first rib resection is logical. It is also safe and effective, with success rates around 85 per cent and few reported complications. First rib removal is also essential in those with cervical ribs[3].

Venous compression leads to congestion or thrombosis by similar mechanisms. Venous pressure measurements and duplex scanning are useful, and can be employed to confirm successful decompression, but two-position venography remains the gold standard. When the patient presents with 'effort' thrombosis, locally directed thrombolysis, heparin anticoagulation and early rib resection is emerging as the optimum treatment, but data are scant[4].

True neurological TOS, caused by compression of the trunks of the brachial plexus, can be diagnosed with confidence[5]. Upper plexus involvement results in deltoid, scapular and occipital pain radiating in the C5/6 or C7 nerve root distribution. Headache and facial pain are common. Lower plexus TOS causes pain in the supraclavicular, medial brachial and ulnar nerve distribution and often coexists with more diffuse aching due to brachial ischaemia. Occipitofrontal tension headache, previously thought to have no clear anatomical explanation, has been shown to be related to spasm in the upper cervical muscles; fibres of rectus capitis posterior minor insert into the occipital dura and can cause headache[6]. Tenderness to palpation over the brachial plexus, tingling on percussion and intrinsic muscle wasting are seen. After operation, grip strength and dexterity should improve, and patients generally report increased temperature and tactile perception. Neurophysiological tests are useful to exclude coexistent pathologies such as peripheral nerve entrapment or cervical radiculopathy; abnormal reflex F wave conduction and decreased sensory action potentials in the medial antebrachial cutaneous nerve may be diagnostic[7]. In the authors' experience, abnormal duplex scanning acts as a 'surrogate marker', as the C8/T1 nerve root closely follows the subclavian artery. Magnetic resonance imaging is useful to exclude cord lesions and radiculopathy, and shows plexus distortion. Lower plexus TOS is treated by first rib and (if present) cervical rib excision. The approach is not important, but a thorough decompression and removal of sufficient rib is vital. Patients with upper plexus symptoms require supraclavicular exploration, radical scalenectomy (scalenotomy is not enough) and possibly rib resection. The pleura is deliberately broached to drain clot into the chest. Endoscopic transthoracic sympathectomy for reflex sympathetic dystrophy can be added with ease and has the advantage of allowing access to the T4 ganglion. Pooled series report success in 85 per cent of patients, with low complication rates and recurrence in 5–10 per cent over 5 years[8].

A 'disputed' form of TOS is described in the American scientific literature. Following neck trauma, a characteristic pain complex is recognized by experienced clinicians, who no longer use the tests which proved equivocal in their early experience. Patients tend to have seen many specialists without a diagnosis being reached. The failure of all treatment contrasts sharply with the good, durable surgical results seen in other forms of TOS but there is, sadly, a lack of independent objective follow-up. Although it has been suggested that the insured patient is more likely to have an operation, results are independent of any associated litigation[9]. It is postulated that scalene muscle spasm in a patient with an anatomical predisposition to develop TOS results in pain and more spasm. Ultrastructural changes in the scalene muscles consistent with this process have been observed. Conservative treatment should be directed towards muscle relaxation, relief of inflammation and attention to posture; this may require a change of occupation as TOS is commoner in those who stoop at work. Aggressive physiotherapy, particularly traction, may make matters worse and a trial of conservative management is essential[10]. Like other surgeons, the authors have operated on only one-third of those initially assessed.

Successful treatment of TOS depends on accurate diagnosis, patient selection and meticulous surgery. Duplex scanning, magnetic resonance imaging and a careful neurophysiological assessment may improve objectivity, and lead to a more widespread appreciation of the different guises of this challenging condition.

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Review

E-cadherin and its associated protein catenins, cancer invasion and metastasis

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E-cadherin is a cell–cell adhesion molecule which is anchored to the cytoskeleton via catenins. There is increasing evidence which suggests that E-cadherin also acts as a suppressor of tumour invasion and metastasis. Both *in vitro* and *in vivo* studies have revealed that expression of E-cadherin correlates inversely with the motile and invasive behaviour of a tumour cell; it also correlates inversely with metastasis in patients with cancer. The function of E-cadherin is highly dependent on the functional activity of catenins. This review summarizes progress, from both basic and clinical research, in our understanding of the roles of E-cadherin and catenins, and discusses the clinical relevance of the discoveries.

For patients with cancer, tumour invasion and metastasis are life-threatening events. In recent years a number of molecules have been identified as suppressors of invasion and metastasis[1–4]; among these is E-cadherin, a cell–cell adhesion molecule. More recently there has been a rapid increase in understanding of the molecular and cellular biology of this molecule and its associated proteins. Furthermore, their role in tumour and metastasis formation is becoming established. This review summarizes recent progress in both basic and clinical research.

E-cadherin and the cadherin superfamily

Cell adhesion molecules (CAMs) are molecules that are involved in cell–cell and cell–matrix adhesions. They may be categorized into cadherins, integrins, the immunoglobulin superfamily and others. Such molecules are key mediators in cell motility and tissue integrity, and are involved widely in morphogenesis and embryogenesis.

Cadherins form a group of cell–cell adhesion molecules which are calcium-dependent transmembrane proteins. They mediate cell–cell adhesion mainly by homotypic interaction, although heterotypic binding between different cadherin molecules is possible. Classical cadherins have conserved repeated amino-acid sequences (cadherin repeats) in their extracellular domain. Based on the structural and functional similarities, cadherins are now recognized as a superfamily composed of an ever increasing number of members[5,6]: (1) cadherins with four cadherin repeats (E- (epithelial), cadherin 4–11[6], B-[7], C-, EP- (homologue to both E- and P-cadherin)[8], N- (neural), P- (placental), R- (retinal)[9], T- (truncated)[10], OB- (osteoblast)[11], K- (kidney)[12], M- (muscle)[13], desmogleins 1–3 and desmocollins 1–3 (desmosomal cadherins)[14,15]); (2) cadherins with more than four cadherin repeats (LI- (liver–intestine)[16], protocadherin (PC) family (PC42 and 43)[17], the *Drosophila* genes *FAT* and *Dachsous*); and (3) others. Sequence similarity between the proto-oncogene *ret* and the cadherin family[18,19] may suggest a new role for the protein encoded by *ret*.

E-cadherin, otherwise known as uvomorulin, L-CAM, cell-CAM 120/80 or Arc-1, is one of the best characterized cadherins and is the main topic of this article. E-cadherin is a 120-kDa transmembrane protein, which is confined to all epithelia originating from ectodermal, mesodermal and endodermal tissue. It is synthesized as a precursor polypeptide (molecular weight 135 kDa), which is processed to the mature polypeptide (120 kDa) shortly after addition of complex carbohydrate groups in the late Golgi complex. The mature form is then delivered to the cell surface. Induction of Ca^{2+}-dependent cell–cell contact results in the rapid localization of surface E-cadherin molecules to the regions of contact, where they form homophilic junctions with neighbouring cells. Structural analysis of cadherin-mediated cell–cell adhesion indicates that cadherins act as a cell adhesion zipper[20]. At the cell surface, E-cadherin is turned over rapidly with a half-life of approximately 5 h. Human E-cadherin is located[21] on chromosome 16q22.1.

Catenins

Catenins are a group of proteins that interact with the intracellular domain of E-cadherin. They are α- (102 kDa), β- (88 kDa) and γ- (82 kDa) catenin. The α-subunit has significant homology to vinculin and the β-subunit to plakoglobin. The β-catenin gene is located on chromosome 3p21 and the α-catenin gene on 5q21–22, regions which have been shown to be involved in the development of certain tumours[22,23]. A novel member of the catenin group[24–26] has been reported recently; this is a new cadherin-associated SRC (Rous Sarcoma virus gene family) substrate ($p120^{cas}$). The protein has been shown to be a tyrosine kinase substrate for epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) receptors. It has four isoforms. The structure, co-location to cadherins and binding partners of p120 are in most aspects similar to those of β-catenin and plakoglobin. The role and function of this new catenin needs to be clarified further.

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Biological role of cadherin–catenin complexes and signal transduction pathways

Formation of E-cadherin–catenin complexes

E-cadherin and catenins form cell–cell adhesion complexes in the cellular membrane (*Fig. 1*). Both β- and γ-catenins bind to newly synthesized E-cadherin before being transported to the plasma membrane; α-catenin binds to E-cadherin or β-catenin–γ-catenin–cadherin complexes at the plasma membrane. All the catenins, and their complexes with E-cadherin or other proteins, form a 'free intracellular pool'. E-cadherin-bound catenin on the plasma membrane can exchange with that in the intracellular pool. It seems that binding of α-catenin to E-cadherin is via its binding to β-catenin[27]. This exchange may form an equilibrium, the balance of which may regulate cell adhesion[28]. Apart from binding to E-cadherin, catenins may bind to each other to form heterodimers (α–β, α–γ)[26,27].

Key role of E-cadherin and catenin in cell–cell adhesion

E-cadherin. The abundant evidence suggesting that E-cadherin is a key cell–cell adhesion molecule for intercellular junctions may be summarized as follows. (1) Cells without E-cadherin expression do not aggregate or adhere to each other and vice versa. (2) E-cadherin is mainly distributed at the cell border and in particular at cell–cell adhesion areas. (3) In cells that express E-cadherin, neutralizing E-cadherin with an antibody and deletion of its encoding gene causes cells to dissociate from each other. (4) Mutation of E-cadherin protein and changing to a low-calcium environment causes cells to dissociate. (5) Transfection of E-cadherin-negative cells with E-cadherin cDNA reverses their non-adhesive status[29,30].

Catenins. The most studied catenin is α-catenin. It binds to E-cadherin and offers a mechanical linkage between E-cadherin and the cytoskeleton. Its normal expression and function are critical for E-cadherin to function normally. Evidence suggests the following. (1) Cells with normal E-cadherin expression but lacking in α-catenin are not able to aggregate or adhere to each other. (2) Deletion of the α-catenin gene, mutation of the α-catenin protein, and mutation of the intracellular domain of E-cadherin, which enables interaction between E-cadherin and α-catenin, results in non-aggregating non-adhesive cells[29].

The role of β-catenin remains controversial. It has been shown that certain motility factors (hepatocyte growth factor, EGF) induce tyrosine phosphorylation of β-catenin, which results in the redistribution of E-cadherin from the intercellular junction to other areas. This leads to increased cell dissociation, motility and invasion[31–34]. In cells transfected with v-*src* oncogene, the increased tyrosine phosphorylation of β-catenin and E-cadherin–catenin complex also leads to disintegration of the cells[35]. It has therefore been proposed that β-catenin may transduce signals for the complex to disintegrate and so facilitate cells to dissociate, although some recent studies do not support this view. Although in some tumour cells E-cadherin may be normally expressed, the dysfunction or mutation of β-catenin may result in a cell–cell disengagement with consequent invasiveness[36]. The gastric cancer cell line HSC-39, which does not compact and aggregate, expresses normal mature E-cadherin, and α- and γ-catenins, but mutated β-catenin. Transfection of normal β-catenin complementary DNA to HSC-39 cells restores normal aggregation. This demonstrates the complex function of β-catenin and warrants further study in the future.

Although the role of γ-catenin is not firmly established, it has been shown that the association of E-cadherin with α- and β-catenin is not sufficient to modify the behaviour of highly malignant cells; γ-catenin is essential in this context[37].

A mechanism involving proteins in the disassembly of the cell–cell junction has been proposed recently[38]. It appears that assembly of cadherin–α-catenin–β-catenin complexes is an early stage in the formation of a cell–cell

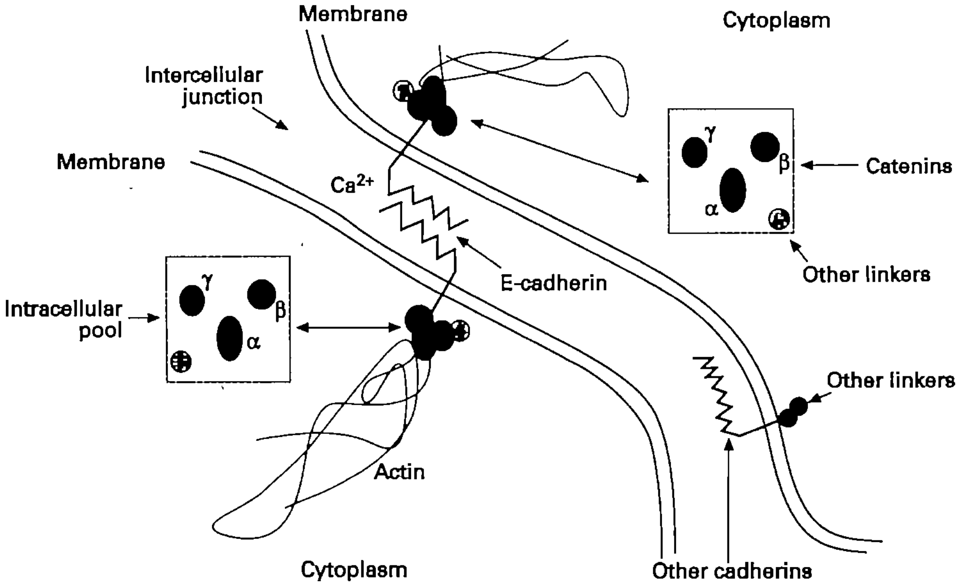

Fig. 1 E-cadherin–catenin complex. E-cadherin binds to α-, β-, γ-catenin and other linker proteins ($p120^{cas}$) and is therefore linked to the cytoskeleton. The complexes bind to each other in a homophilic interaction and play a key role in cell–cell adhesion. This interaction is dependent on extracellular calcium levels. Catenins bound to E-cadherin may exchange with their intracellular pool

junction, but the mature form of the junction requires the participation of plakoglobin. When the cell migrates, plakoglobin must dissociate first to allow the cadherin–α-catenin–β-catenin complex to disassemble. Overall, functional catenins are a key requirement for normally functioning E-cadherin[36,39].

E-cadherin complexes and other cellular functions

E-cadherin may also be involved in the transportation of intestinal peptide[40]. Activation of the E-cadherin system also reduces the growth of tumour cells[41].

Role of E-cadherin and catenin in tumour motility, invasion and metastasis: *in vitro* studies

A number of studies have established that E-cadherin and α-catenin are molecules that suppress tumour invasion and metastasis.

Loss of cell–cell adhesion, and gain in motility and invasiveness

There are a few *in vitro* studies showing the relationship between E-cadherin–catenins and tumour cell motility and invasiveness. Manipulation of E-cadherin[42–49], α-catenin[50,51], β-catenin[36] and γ-catenin, by means of antibodies, gene deletion or mutation, genetic engineering, functional modification, microinjection and antisense techniques, provides evidence that abnormalities of these proteins facilitate tumour cell dissociation, and increase motility and invasiveness. A clear *in vitro* model has shown that a cell without E-cadherin, or with dysfunctioning E-cadherin, is easily washed off a main tumour mass by lymphatic or venous shear forces[52]. All of the above modifications facilitate the establishment of distant metastases.

Modification of tumour cell differentiation by E-cadherin

A monoclonal antibody (human E-cadherin-1), specific for human E-cadherin, inhibits up to 75 per cent of the glandular differentiation of human colonic carcinoma cell line SW1222 growing in collagen gel[53].

E-cadherin and matrix degradation enzymes

Removal of E-cadherin with antibodies results in differentiated cancer cells losing their epithelioid morphology and gaining invasiveness. This is accompanied by a marked increase in urokinase-type plasminogen activator (uPA) which facilitates the invasion. This increase probably involves RNA and protein synthesis[54]. E-cadherin is also associated with the distribution of uPA; increased calcium concentration together with functioning E-cadherin may mobilize the distribution of uPA from the perinuclear region to the cell surface[55].

Association with other tumour-related products

Shibata and colleagues[56] showed that plakoglobin also associates with the adenomatous polyposis coli (APC) protein, and that tyrosine phosphorylated plakoglobin associates with cadherins but not with APC. The recent surprising discovery that β-catenin forms a protein–protein complex with a tumour suppressor gene (*APC*) product has added further to the importance of this protein in tumour metastasis[57,58]. It has also been confirmed recently that APC competes with E-cadherin in binding to β-catenin, and that this interaction may sequester negative regulatory variants of β-catenin and prevent their interaction with E-cadherin[59]. The frequent mutation or deletion of the *APC* gene in colorectal cancer may, therefore, damage this relationship[60,61]. Catenins also associate with the c-*erb*B2 gene product, an oncogenic protein tyrosine kinase[63]. There is, furthermore, a close correlation between the expression of E-cadherin and the thyrotrophin receptor in thyroid cancer[64].

Expression of E-cadherin and catenins in human tumours

Levels of E-cadherin–catenins in human cancer

E-cadherin. Expression of E-cadherin has been studied in most human cancers (*Table 1*). Tumours generally show less expression than normal or even a complete absence of expression of the molecule. A recent study[105] revealed that, in the case of colon, there is a steady decrease in the expression of E-cadherin through normal mucosa, adenoma, primary cancer and metastatic lesions, indicating the critical involvement of the molecule in the progression of the disease.

α-Catenin. Studies on α-catenin have revealed an overall reduction in expression of the molecule in most cancer types (*Table 2*).

Others. A HSC-39 gastric cancer cell line which expresses normal mature E-cadherin, and α- and γ-catenins, has a mutated β-catenin[36]. Otherwise there are no reports on β- and γ-catenins in human cancer.

Co-expression of E-cadherin and catenins

That E-cadherin and catenins are critical in terms of cell–cell adhesion and tumour invasion has highlighted the importance of studying the co-expression of these molecules in human tumours. Reports of such studies have accumulated quickly, but these are mainly of the co-expression of E-cadherin and α-catenin. Such studies suggest that detection of the combination of E-cadherin and α-catenin is a better marker for predicting local spread and systemic metastasis.

Matsui *et al.*[107] showed that α-catenin expression was reduced in 70 per cent of gastric cancers; this was significantly related to dedifferentiation, depth of invasion, infiltrative growth and lymph node metastasis. Studies of co-expression of α-catenin and E-cadherin showed that 28 per cent of tumours preserved normal levels of both molecules, 55 per cent had reduced levels of both, and 15 per cent exhibited an α-catenin-negative–E-cadherin-positive state. Lymph node involvement is associated with 82 per cent of tumours showing no α-catenin and E-cadherin expression, compared with 67 per cent of α-catenin-negative–E-cadherin-positive lesions and 24 per cent of tumours expressing both molecules. This study also revealed that α-catenin, or the combination of α-catenin and E-cadherin, is a better indicator of liver metastasis. Co-expression of E-cadherin and α- and β-catenins in gastric cancer has been studied by Yasui *et al.*[76]; a reduced level of E-cadherin, α-catenin and β-catenin was reported. The levels of E-cadherin and

Table 1 Expression of E-cadherin in tumour cell lines and tumour tissues

Origin	Cell line	Human tumour tissue
Colon	Normal: Colo205, SW620, HCT116A[47]	Reduced[62,72,73]
	Low: HT29, HCT116B and Ls174T[47,65]	Normal: well differentiated tumours[72,73]
	Variable: Clone A, MIP 101, RKO, CCL222, CCL228[51,53]	Negative: poorly differentiated or with metastases[72,73]
	High: CX-1, CCL235, CCL187, DLD-2, HRT18, SW1222[51,53,65,66]	
Stomach	Strong: HSC39 and MKN-28[36]	No gross alteration[74]
	E-cadherin gene mutation: MNK45, KATO-III[67]	Reduced or absent[76–78]
		Gene mutation[79]
Pancreas	—	Pancreatic cancer: absent[80]
Liver	Reduced in a number of cell lines[48]	Reduced or completely absent[48]
Oesophagus	—	Disorganized[68] or reduced[68,81]
Lung	Positive: Cor L23[66]	Normal: well differentiated SCC and adenocarcinoma[68]
	Negative: A549, A427, SK LU 1[66,68]	Reduced: poorly differentiated SCC and SCLC[68,82]
		Redistributed[62]
Bladder	—	Reduced[83,84]
Breast	Positive: MCF7, T47D, VHB1, ZR751[66,69]	Normal: well differentiated carcinomas[86]
	Negative: MDA MB231[66,69]	Reduced: infiltrating, poorly differentiated, late-stage carcinoma[86–89]
		Completely absent: invasive lobular and infiltrating carcinomas[86,90]
		Absent: tumours with metastasis[89]
Prostate	Reduced: LNCaP, DU145, PC-3, PPC-1, TSU-Prl, DuPro[70]	Reduced[70,91,92]
		Absent: advanced and poorly differentiated carcinomas[92]
Uterus	—	Reduced: invasive and metastatic tumours[93]
		Mutation and LOH[94]
Skin	Positive: G361[66]	Normal: superficial and nodular basal cell carcinoma[95]
	Negative: M19[66]	Reduced: infiltrative basal cell carcinoma[95]
Ovary	—	Mutations and LOH[94]
		Reduced. metastatic cells[96]
Thyroid	—	Varies from normal to completely absent[64]
Other	Positive: HN6, SCC15, RT112[71]	Gingival cancers: reduced or completely absent[97]
	Negative: GEE, HN5, B_2A_4, GBi2A[71]	Head and neck SCC: reduced[98]
		Kidney: reduced depending on tumour type and grade[99,100]
		Oral cancer: reduced[101]
		Glucagonomas: absent[102]
		SCC. reduced or absent[103,104]

SCC, squamous cell carcinoma; SCLC, small cell lung cancer; LOH, loss of heterozygosity

Table 2 Expression of α-catenin in human cancer cell lines and tumour tissues

Origin	Cell line	Human tumour tissue
Oesophagus	—	Reduced, absent or normal[81,106]
Lung	—	Normal α-catenin mRNA[68]
Breast	—	Variable[85]
		Reduced: sirrhous adenocarcinoma[63]
Prostate	Reduced: LNCaP, DU145, PPC-1, TSU-Prl, DuPro[70]	Reduced[70]
	Absent: PC-3[70]	
Colon	Reduced: Clone A, MIP 101, RKO, CCL222, CCL228[51]	Reduced or completely absent[106]
	High level: CX-1, CCL235, DLD-2, CCL187[51]	
Stomach	—	Reduced or completely absent[75,76,106,107]

mRNA, messenger RNA

α-catenin are principally related to the invasion and progression of these tumours.

These co-expression studies reveal that the expression of E-cadherin and catenin can be both normal[85], both reduced[70,85], both completely lost[85], normal for E-cadherin but altered for catenins[70,81,106], and altered for E-cadherin but normal for catenins[68].

Patterns of abnormalities of E-cadherin and catenins

Tumour cells behave abnormally with respect to E-cadherin and catenins, as shown in *Fig. 2*.

Reduced or complete loss of expression. This is perhaps the most frequent pattern seen in human tumours. Loss of expression of E-cadherin has been shown in over 18 per cent of gastric cancers[75] and in hepatocellular carcinoma[48]; reduced expression or complete loss of expression has been noted in gingival cancers[97].

Mutation. This has been reported recently by different groups[67,79,108]. The first case of human cancers was from Becker *et al.*[108], who showed that there is in-frame skipping of exon 8 or 9 and deletion of exon 10 in patients with diffuse-type gastric cancer. Such mutation was noted

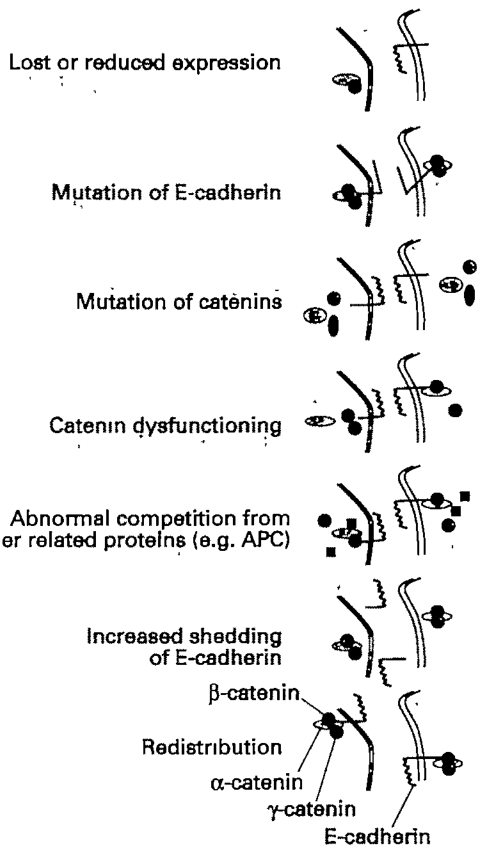
Lost or reduced expression
Mutation of E-cadherin
Mutation of catenins
Catenin dysfunctioning
Abnormal competition from other related proteins (e.g. APC)
Increased shedding of E-cadherin
β-catenin
Redistribution
α-catenin
γ-catenin
E-cadherin

Fig. 2 Schematic demonstration of pathological changes of E-cadherin–catenin complexes in tumour cells. APC, adenomatous polyposis coli

in over half the diffuse types studied and in 14 per cent of mixed cancers. Mutation of α-catenin in the cancer cell has also been reported by Oda *et al.*[67]: a mutated α-catenin will not function as a proper linkage for E-cadherin. Overall, these observations include DNA mutations around exon–intron junctions, loss of the wild-type allele of E-cadherin locus and abnormal messenger RNA (mRNA) expression. Somatic non-sense, somatic mis-sense, and mis-sense mutations with somatic loss of heterozygosity have been identified in endometrial and ovarian cancers[94].

Disorganized or redistributed. This is demonstrated as an altered pattern of staining with cytoplasmic expression or variable staining in different areas inside a tumour. It is typically found in oesophageal cancer[68]. Spotty or diffuse distribution of E-cadherin has been noted in poorly differentiated lung cancer[82]. There is an increased intracellular distribution of E-cadherin (instead of on the cell surface) in thyroid cancer[64]; there is also an abnormal distribution within the cytoplasm in breast carcinoma[90]. An increased cytoplasmic staining of E-cadherin occurs in some adenocarcinomas and in some squamous cell carcinomas[109]. Boyer *et al.*[110] reported that fibroblast growth factor-induced motility and dissociation of tumour cells is related to the redistribution of E-cadherin over the entire cell surface and within the cytoplasm.

Shedding from the cell surface. Katayama *et al.*[111,112] have recently reported that patients with cancer may have a markedly increased urinary excretion of soluble E-cadherin, resulting from shedding of the molecule from the cell surface. Original tumours (rather than metastases) have a rather low expression of the molecule. Such observations have been made in liver, gallbladder, colon, lung and gastric cancers. Urinary excretion has also been shown by other workers in bladder cancer[113].

Competition from other proteins. Other molecules, such as the *APC* gene product, may also compete for binding to E-cadherin and so damage the normal E-cadherin–catenin interactions, resulting in the abnormal function of E-cadherin[57–61].

E-cadherin–catenins and tumour differentiation

E-cadherin is a differentiation marker[114] in thyroid cancer[64,114], squamous cell carcinoma[98,104], endometrial carcinoma[93] and gastric cancer[77]. The expression of E-cadherin varies with different grades and pathological types; for example, infiltrating lobular carcinoma of the breast has a very low level of E-cadherin, infiltrating ductal carcinoma has a reduced level, and papillary and colloid carcinomas have normal levels[87]. E-cadherin expression correlates with high biological grade and lack of steroid hormone receptors in these tumours[87].

E-cadherins–catenins and metastasis

Ochiai[75] recently reported the interesting observation that human lobular carcinoma infiltrates the stroma as single cells which have no E-cadherin or α-catenin expression. This leads to the hypothesis that, in a tumour mass, cells with low or no E-cadherin or catenin expression will leave the main tumour body and initiate the metastatic cascade.

Indeed, studies on human cancer confirm the relationship between these molecules and metastasis. Reduction of E-cadherin expression is frequently noted in invasive ductal carcinomas, poorly differentiated carcinomas, T_{3-4} tumours, tumours with extensive lymph node metastasis, and those with distant metastasis[89]. E-cadherin levels vary from normal to zero in thyroid cancer. The expression of E-cadherin in relapsing thyroid carcinoma and in tumours with metastatic spread is, irrespective of histiotype, low or totally lacking[64]. The relationship between E-cadherin–catenins and local spread or distant metastasis has also been reported in liver tumours[48], ovarian tumours[96], invasive breast cancer[115], pancreatic cancer[80], endometrial carcinoma[92] and renal cancer[100].

The relationship between co-expression of E-cadherin and α-catenin and clinical profile has been reported in patients with breast cancer by Takayama *et al.*[85]; lymph node metastasis was seen in 80 per cent of patients with E-cadherin-negative–α-catenin-negative tumours and in 40 per cent of those with E-cadherin-positive–α-catenin-positive lesions.

E-cadherin–catenin and other tumour-related molecules

It has been shown that, in prostatic tumours, reduced E-cadherin mRNA levels are associated with increased mRNA levels of β1 and α5 integrins and fibronectins[116]. In patients with bladder cancer, there was an inverse relationship between the expression of E-cadherin and autocrine motility factor receptor; the motility factor is produced by cancer cells and stimulates tumour cell motility and invasion. The reduction in E-cadherin expression and concomitant increase in gp78 expression was associated with poor prognosis (rapid cancer progression and shorter survival), suggesting that a reduction in E-cadherin expression is associated with an increase in the level of gp78 in bladder cancer; this may define a high-risk group of patients[84].

E-cadherin–catenins and prognosis

Although there has been some speculation about the relationship between E-cadherin levels and long-term survival, so far there are no studies indicating a long-term relationship, mainly because of the short time since the discovery of the molecule. By using an *in situ* hybridization technique to measure mRNA, Dorudi *et al.*[117] have shown that patients who survive for more than 5 years have significantly higher levels of E-cadherin mRNA than those who survive for less than 5 years. Such a relationship has also been reported in patients with head and neck squamous cell carcinoma[98], bladder cancer[83], gastric tumours[77] and prostate cancer[91,118].

Modulation of the expression of the proteins

Modulation of the expression of E-cadherin and catenins is less well explored. However, there are some recent studies suggesting a means of regulation (*Table 3*). Vandenbossche *et al.*[131] reported recently a host regulation of E-cadherin expression by as yet unidentified factors; it was found that when non-invasive cells which express normal levels of E-cadherin are injected into the body, they undergo a reversible loss of expression of E-cadherin and gain invasiveness. This may be due to their contact with host cells or to regulation by host factors. Expression of wild-type *APC* gene caused a pronounced reduction of β-catenin concentration, particularly its intracellular pool, at a post-translational level, presumably by increased degradation of β-catenin[132]. In contrast, transfection with the *Wnt*-1 oncogene increased the accumulation of β- and γ-catenins, increased the binding of β-catenin to cadherin and strengthened calcium-dependent cell adhesion[133]. The E-cadherin promoter is not active in non-expressing cells; this may result from binding of a repressor protein to the promoter[134]. Studies on the regulation of expression of the complex are accumulating and more mechanisms are being identified; some of them may have clinical importance.

Expression of E-cadherin and catenins in other diseases

It has been reported recently that in some cases of colonic Crohn's disease there is a reduced expression of E-cadherin[62]. E-cadherin plays an important role in basic morphogenesis in the development of a multicellular organism and in the biogenesis of epithelium[135]. Heasman and colleagues[136] have shown abnormal expression of both cadherin and α-catenin in developmental abnormalities. E-cadherin is required for the formation of extended bile canaliculi networks, which are necessary for the function of the liver[137]. All of these examples point to the importance of the complex in normal physiology as well as in the pathological context.

Problems, challenges and prospectives

Although significant progress has been made in this area, there are gaps to be narrowed. First, the co-expression of cadherin and catenins, particularly β- and γ-catenin, needs more extensive study. In most reports E-cadherin was the only molecule examined; a limited number of other studies examined only α-catenin together with E-cadherin. Reports on β- and γ-catenin are very limited. As the roles of p120 protein and *APC* gene product in cadherin–catenin function become clear, their expression in human tumours should also be investigated alongside that of E-cadherin and catenins. Knowledge of the expression of these molecules will reveal further their role in tumour metastasis and invasion.

Second, regulation of the interaction of E-cadherin and catenins needs to be explained further. Although the loss of E-cadherin and/or catenin leads to increased cell dissociation and motility and/or invasion, certain factors may cause cells to dissociate and move without apparent change in E-cadherin and catenin activity. This leads to

Table 3 Regulation of expression of E-cadherin

Material	Effects on E-cadherin expression	Reference
Dibutyryl cAMP	Increased on MCF7 cells	119
M_3 muscarinic cholinergic receptor	Increases the binding capacity of E-cadherin	120
Epiglycanin	Inhibits E-cadherin–catenin complex function by masking	121
IGF-1	Activates E-cadherin in breast cancer cells	122
EGF receptor activation	Enhances expression of E-cadherin	123
LMP (EBV-encoded membrane protein)	Reduces expression of E-cadherin	45
v-*src* transfection	Increases phosphorylation of E-cadherin–β-catenin complex	35
Anti-*N*-acetylgalactosaminylphosphotransferase	Reduces cadherin-mediated cell–cell adhesion	124
ERBB2 receptor transfection	Decreases E-cadherin level	125
17-β oestradiol	Increases E-cadherin mRNA level	126
Tamoxifen and metabolites	Restores E-cadherin function in MCF7/6 cells	127
Retinoic acids	Increase E-cadherin in the SK-BR-3 cell line	128
High-calcium environment	Increases E-cadherin expression on MCF7 cells	69
γ-Linolenic acid	Increases E-cadherin expression	65, 66
Phorbol ester (PMA)	Reduces E-cadherin expression	129
Interleukin 6, EGF, HGF/SF	Redistribution of E-cadherin	32, 130

mRNA, messenger RNA; cAMP, adenosine 3'-5'-cyclic monophosphate; IGF, insulin-like growth factor; EGF, epidermal growth factor; LMP, latent membrane protein; EBV, Epstein–Barr virus; PMA, phorbol myristate acetate; HGF, hepatocyte growth factor; SF, scatter factor

the hypothesis that such factors may modify the function of the complex, resulting in reduced cell–cell adhesion. Recent work from Brady-Kalnay *et al.*[138] indicates that tyrosine phosphorylation and dephosphorylation can be regulated by cytokines and protein tyrosine phosphatase. This balance of dephosphorylation and phosphorylation correlates with less adhesive and highly adhesive cell function respectively. This may open a new area of research into means of regulating the function of the E-cadherin–catenin complex, which may lead to the identification of novel pathways of intervention of clinical importance.

Third, the functional state of catenins (e.g. tyrosine phosphorylation) in human tumours should be examined and an attempt made at wider detection of mutations of these proteins (both in more tumour types and examining other catenins). This may also be useful in identifying promising agents which may be used to manipulate the expression of these molecules in clinical situations. There has been a steady increase in the number of agents that can upregulate the E-cadherin complex. Some may have a future in clinical practice. The genetic approach should also be considered as a means of restoring the normal function of the complex.

Overall, E-cadherin and α-catenin are molecules that suppress tumour invasion and metastasis. They are either underexpressed or mutated in human cancers. There is a strong inverse relationship between reduction in expression of these molecules and poor prognosis in patients with cancer. Efforts should be made to explore any means of regulating or restoring the function of the cadherin–catenin complex in clinical practice.

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Review

Arterial therapy of hepatic colorectal metastases

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Considerable experience of the treatment of irresectable hepatic colorectal metastases has accumulated over the past three decades. In this review, the rationale for hepatic artery treatment of colorectal metastases to the liver is presented and various access techniques and chemotherapeutic agents for infusion are discussed. Randomized trials of hepatic artery chemotherapy (HAC) are analysed, and the promising results of recent studies combining less toxic and more effective agents are summarized. Continuous infusion pumps provide the most reliable and long-lasting access for HAC. Appropriate surgical techniques and medical management can minimize complications. Although tumour progression is best controlled by HAC, a clear-cut survival advantage has yet to be demonstrated. While hepatic artery infusion chemotherapy cannot yet be recommended outside investigational protocols, the experience gained so far should stimulate further studies.

Colorectal cancer is one of the most devastating malignancies in developed countries, with an age-adjusted annual mortality rate worldwide of up to 31 deaths per 100000 men and 21 per 100000 women[1]. In the Western hemisphere, this incidence is surpassed only by that of lung and breast cancer. In the USA it was estimated that 138000 patients would be newly diagnosed with colorectal cancer in 1995[1]. Of these, approximately 20 per cent would present with or develop metastases confined to the liver during the course of the disease[2,3]. Left untreated, hepatic colorectal metastases carry a dismal prognosis. Six studies of the natural history of such metastases, reporting on a total of 1151 patients, described a 5-year survival rate equal to or less than 3 per cent[4–9]. In one-third to one-half of these patients, hepatic resection offers an opportunity for cure, with a 25–39 per cent 5-year survival rate[8,10–13].

The role of chemotherapy in the treatment of colonic cancer has evolved in the past decade. In 1990, Moertel and colleagues[14] reported a reduction in the recurrence rate, as well as a survival benefit, in patients treated with adjuvant 5-fluorouracil (5-FU) and levamisole following resection for Dukes C colonic primaries. Other studies have confirmed the potential benefits of chemotherapy in the adjuvant setting after resection of both Dukes B2 and C primary colorectal cancer[15–17]. In contrast, the role of chemotherapy in metastatic colorectal cancer is not clearly established[18]. For patients with metastatic colorectal cancer confined to the liver and not amenable to resection, there is presently little hope for meaningful palliation, prolonged survival or cure, since the response rate of hepatic colorectal metastases to conventional systemic chemotherapy is only 18–28 per cent[19–21].

In an attempt to improve on these rather dismal results, hepatic artery chemotherapy (HAC) has been explored for the treatment of hepatic colorectal metastases; this has continued over 45 years[22–25]. High-dose regional chemotherapy directed exclusively at the metastatic organ should lead to increased response rates while limiting the systemic side-effects, with the hope that this would ultimately translate into improved survival. The tenets supporting HAC are: (1) hepatic metastases more than 3 mm in diameter derive their blood supply from the hepatic artery and not the portal vein[26,27]; (2) radiolabelled [^{3}H]floxuridine (FUDR) concentrates 15-fold in hepatic metastases when injected through the hepatic artery as opposed to the portal vein[28] and 400-fold over systemic infusion[29]; and (3) certain chemotherapeutic agents are almost completely extracted during first pass through the liver, allowing large doses to be given with minimal systemic effects[30].

In this article, techniques and agents used for HAC of hepatic colorectal metastases are reviewed. Specifically, the various routes of access for HAC, the technical complications of implantable devices, the development of new chemotherapy regimens, the randomized trials exploring HAC and the future prospects of combined modalities (cryotherapy and HAC, embolization and HAC, resection and HAC) are discussed.

Hepatic artery access

Several approaches have been used to deliver HAC: (1) angiographically placed hepatic arterial catheters, (2) surgically implanted infusion ports used with external pumps and (3) surgically implanted infusion pumps.

In the initial trials of HAC monthly percutaneous hepatic artery catheterization and infusion of chemotherapy was employed with varied success. While this was a minimally invasive technique, technical complications of repeated arterial puncture, poor patient acceptance because of high rates of catheter migration, and the need for hospitalization and confinement to bed limited its use[31]. Several reports indicated that more than one-third of patients did not complete an adequate trial and the duration of adequate intra-arterial access ranged from only 2 to 7 months[32–36]. This approach has recently been re-evaluated; it has been found that the cost of more than three treatments exceeds the combined price of a totally implantable pump and its placement[37].

Arterial ports combined with an external pump for delivery of chemotherapy for a period of 4 days to 2 weeks per month have also been used[38,39]. Ports are attractive because of their low cost and small size. However, they

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require a laparotomy for arterial cannulation, a similar procedure to that required for the placement of an infusion pump. The chief complication with a port is the 30–42 per cent incidence of catheter or hepatic artery thrombosis[40,41] requiring cessation of treatment in more than 20 per cent of patients[39]. In a study comparing port and pump, the mean duration of hepatic artery patency was 9 months with a port and 28 months with an implantable continuous infusion pump[42].

HAC was advanced by the development of totally implantable infusion pumps in the 1980s[43–45]. Buchwald *et al.*[46] initially treated five patients with FUDR. Since then the implantation of non-programmable (Infusaid 400; Strato/Infusaid, Norwood, Massachusetts, USA) or programmable (Syncromed; Medtronic, Minneapolis, Minnesota, USA) infusion pumps has been selected by many as the preferred method of delivery of hepatic chemotherapy[3,47–49]. Non-programmable pumps are used unless specific chemotherapy schedules are needed. The Infusaid 400 pump, which has a sustained-release mechanism as well as a side port allowing for bolus intra-arterial injection of imaging agents for radionuclide scanning or angiography and chemotherapeutic agents, has been used in six randomized studies discussed later in this review[3,47,50–53].

In patients with irresectable metastases apparently localized to the liver, a careful evaluation should take place before pump or port implantation. To optimize the efficacy of chemotherapy and minimize complications, HAC should be directed to the entire liver, without extrahepatic perfusion. The anatomy is delineated before operation with selective hepatic, coeliac and superior mesenteric arteriograms. Computed tomography (CT) of chest, abdomen and pelvis, and colonoscopy, if indicated, are performed to exclude extrahepatic disease, as up to 19 per cent of patients with disease apparently confined to the liver will have unsuspected extrahepatic metastases[54].

If technically possible, a laparoscopy is first performed to rule out extrahepatic disease[55,56]. A thorough exploration is then performed at laparoscopy to confirm the absence of extrahepatic disease. Portal nodes are sampled and any other suspicious node or extrahepatic tumour site is sent for frozen-section histology. The presence of extrahepatic disease has been considered a contraindication to HAC, although pumps have been implanted in some patients with minimal extrahepatic spread, especially in those in whom systemic chemotherapy has failed[50,52,57]. Between 55 and 76 per cent of patients have classic hepatic arterial anatomy[58], and the port or pump catheter is implanted in the gastroduodenal artery with the tip located at the junction between the hepatic and the gastroduodenal artery. Between 2 and 3 cm of the proper hepatic artery is dissected and the branches ligated for the purpose of reducing common bile duct, gastric and pancreatic perfusion, a potential cause of complications. Likewise, the right gastric artery is ligated. Details of the technique of pump and port implantation, and the pitfalls encountered in the presence of anatomical variants, have been summarized recently elsewhere[59]. In the presence of a dual arterial blood supply, dual-lumen pump/ports have been recommended[60,61], but the need for such equipment has been questioned since cross-perfusion of the liver has been shown to occur eventually after ligation of the replaced hepatic artery[40]. Cholecystectomy is performed routinely to prevent chemical cholecystitis[62]. A port or pump side-port injection of fluorescein allows immediate assessment of the distribution of the perfusate. Complete hepatic perfusion is confirmed with a Wood's lamp and any misperfusion can be identified and addressed immediately. Alternatively, port or side-port injection of methylene blue or other injectable dyes may be used. The hepatic perfusion is retested with radionuclide scans after surgery and before chemotherapy is initiated. Comparison of a standard technetium-99m sulphur colloid scan of the liver and spleen with a technetium-99m macroaggregated albumin (TcMAA) (0·5 μCi) infusion via the port or pump side port will identify perfusion mismatches (incomplete hepatic or extrahepatic perfusion).

In patients whose liver metastases are diagnosed synchronously, complete resection of the primary tumour and pump placement may be undertaken at the same operation, provided that the non-contaminated part of the procedure is performed first and the pump and catheter are excluded from the surgical field. A recent study has confirmed that this is a safe and cost-effective approach to patients presenting with synchronous disease[47].

Technical complications

One of the main objections to HAC is the morbidity associated with the technical complications of port and pump implantation. The mortality rate associated with pump and/or port placement is less than 1 per cent. One study reported no deaths in 180 patients with pump and/or port placement[40], while another reported two deaths (0·7 per cent) after placement of 303 hepatic artery pumps[63]. Technical complications of pump implantation from large series are reviewed in *Table 1*. These complications are not consistently reported in all studies; two randomized studies failed to report technical complications altogether[50,71]. Two studies from large institutions with experience of pump implantation specifically reported on the morbidity associated with pumps[40,63]. In these reports the cumulative complication rate for pump implantation or pump use was 12–33 per cent. Pump malfunction is rare (0·7 per cent) with non-programmable continuous infusion pumps. While pump pocket haematomas and/or seromas are not uncommon (6 per cent), they can frequently be treated by needle aspiration and drainage of the collection. Recurrent haematomas may necessitate moving the pump to another site. Pump pocket infections are rare (1 per cent) and require removal of the pump but the hepatic artery access can be preserved by connecting the catheter to an arterial port to allow further chemotherapy to be given.

Finally, placement of hepatic artery catheters is a complex technical procedure requiring experience. In a review of complications of pump implantation, the incidence of technical errors correlated with the surgeon's experience; there was a fivefold increase in problems when the surgeon had independently placed fewer than ten pumps previously[59]. In the same study, the placement of dual-lumen pumps in patients with anomalous hepatic arterial anatomy was associated with a technical complication rate greater than 20 per cent, regardless of the surgeon's experience[59].

Chemotherapeutic agents

HAC is used to deliver high concentrations of chemotherapeutic agents to tumour cells while minimizing systemic exposure. Ideally, drugs used in HAC should

Table 1 Technical complications of hepatic artery chemotherapy with implantable pumps

Reference	Year	No. of patients	Skin breakdown	Catheter break, misplacement, migration, leak or kink	Pump pocket infection	Pump pocket haematoma or seroma	Catheter–artery thrombosis or aneurysm	Pump malfunction
Non-randomized studies								
Cohen *et al.*[57]	1983	50	—	1 (2)	1 (2)	—	0 (0)	0 (0)
Johnson *et al.*[64]	1983	26	—	0 (0)	0 (0)	3 (12)	0 (0)	0 (0)
Weiss *et al.*[65]*	1983	21	—	1 (5)	0 (0)	1 (5)	0 (0)	0 (0)
Kemeny *et al.*[66]	1984	41	—	—	—	—	—	—
Niederhuber *et al.*[67]	1984	93	0 (0)	1 (1)	1 (1)	2 (2)	3 (3)	0 (0)
Schwartz *et al.*[68]†	1985	30	—	2 (7)	1 (3)	6 (20)	0 (0)	—
Shepard *et al.*[69]	1985	62	2 (3)	0 (0)	0 (0)	—	0 (0)	0 (0)
Balch and Urist[70]	1986	110	—	0 (0)	0 (0)	—	0 (0)	0 (0)
Curley *et al*[40]	1993	143	1 (0·7)	21 (14·7)	1 (0·7)	19 (13·3)	16 (11·2)‡	2 (1·4)
Kemeny *et al.*[61]	1994	303	0 (0)	14 (4·6)	2 (0·7)	1 (0·3)	14 (4·6)	2 (0·7)
Total		879	3 of 601 (0·5)	40 of 838 (4·8)	6 of 838 (0·7)	32 of 616 (5·2)	33 of 838 (3·9)	4 of 808 (0·5)
Randomized studies								
Chang *et al*[50]	1987	24	—	—	—	—	—	—
Kemeny *et al*[3]	1987	48	1 (2)	2 (4)	—	—	—	—
Hohn *et al.*[51]	1989	67	—	9 (13)	1 (1)	—	—	—
Martin *et al*[52]	1990	33	2 (6)	—	2 (6)	—	5 (15)	2 (6)
Wagman *et al.*[71]	1990	40	—	—	—	—	—	—
Rougier *et al.*[53]	1992	81	2 (2)	1 (1)	—	12 (15)	10 (12)	—
Allen-Mersh *et al.*[47]	1994	51	—	5 (10)	3 (6)	—	—	0 (0)
Total		344	5 of 162 (3·1)	17 of 247 (6·9)	6 of 151 (4·0)	12 of 81 (15)	15 of 114 (13·2)	2 of 84 (2)
All studies		1223	8 of 763 (1·0)	57 of 1085 (5·3)	12 of 989 (1·2)	44 of 697 (6·3)	48 of 952 (5·0)	6 of 892 (0·7)

Values in parentheses are percentages. *includes four patients with non-colorectal hepatic malignancy; †includes five patients with non-colorectal hepatic malignancy; ‡includes seven thromboses or occlusions in 21 programmable pumps

have: (1) a steep dose–response curve in the target tumour cells so that a maximal effect may be produced by increasing the regional drug level; (2) minimal intrinsic hepatotoxicity; (3) high hepatic extraction; and (4) rapid total body clearance to avoid systemic side-effects. Drugs expressing such characteristics include FUDR and, to a lesser degree, 5-FU and doxorubicin[29,30].

Infusion therapy with the pyrimidine antagonists 5-FU and FUDR has been the focus of most clinical regional chemotherapeutic efforts. These drugs are so efficiently extracted that the high hepatic arterial flow rate (150–1000 ml/min) is not a problem[72]. Total body clearance is extremely high with FUDR (25 000 ml/min) and 5-FU (4000 ml/min). In the liver, the first-pass extraction for FUDR is 94–99 per cent and for 5-FU 19–51 per cent[30]. 5-FU is phosphorylated to FUDR and subsequently to the active metabolite fluorodeoxyuridine monophosphate. FUDR is limited in its systemic use because of rapid *in vivo* degradation. FUDR and 5-FU have been central in HAC because of this appealing biological profile and because they are the only agents currently available with significant activity in colorectal cancer.

Leucovorin, dexamethasone, mitomycin and cisplatin have also been studied in HAC. Leucovorin has proved effective in combination with 5-FU as systemic treatment but must be used at a lower dose (15 mg per m^2 per day for 14 days) than usual (20–300 mg per m^2 per day for 5 days) when included in HAC regimens to avoid excessive hepatobiliary toxicity[73–75]. The addition of dexamethasone to FUDR and leucovorin has resulted in fewer hepatobiliary side-effects and a better response rate[76]. Mitomycin, cisplatin and bischloroethylnitrosourea have been variously used in combination with FUDR in an effort to overcome *de novo* or acquired resistance of tumour to FUDR[67,69,77]. The response rate for hepatic arterial FUDR and mitomycin was reported initially to be considerably higher than that for systemic administration. However, when more restrictive and defined criteria of response were used the combination regimen did not show a dramatic difference compared with FUDR alone. All randomized trials with continuous infusion pumps have used FUDR alone.

Recently, Arisawa *et al.*[78] have reported that short-term intrahepatic FUDR combined with bolus administration of mitomycin reduced the risk of developing drug resistance and produced an effect similar to long-term FUDR therapy in an animal model. This result warrants further study. Additional studies of FUDR combined with interferon γ[79], interleukin 2[80] and tumour necrosis factor[81] have been reported. These regimens need further testing before phase III studies can be conducted.

Complications of chemotherapy

Toxic complications of hepatic artery infusion are summarized in *Table 2*. This method of infusion of FUDR or 5-FU does not normally produce systemic side-effects such as myelosuppression, mucositis or diarrhoea. When systemic side-effects occur, possible shunting of chemotherapeutic agents should be considered. Kaplan *et al.*[82] evaluated TcMAA hepatic radionuclide scans, and correlated diarrhoea with the presence of shunting to the lungs. When the shunting of TcMAA from hepatic artery to lung was below 15 per cent most patients had no gastrointestinal toxicity. However, when shunting was

Table 2 Toxicity of hepatic arterial chemotherapy with implantable pumps

Reference	Year	FUDR dose (mg per kg per day)	No. of patients	Gastritis, nausea or vomiting	Ulcer	Diarrhoea	Sclerosing cholangitis
Non-randomized studies							
Cohen *et al.*[57]	1983	0·3	50	—	8 (16)	—	—
Johnson *et al.*[64]	1983	—	26	—	—	2 (8)	—
Weiss *et al.*[65]	1983	0·2–0·3	21	9 (43)	1 (5)	2 (10)	—
Kemeny *et al.*[66]	1984	0·2–0·3	41	12 (29)	12 (29)	0 (0)	2 (5)
Niederhuber *et al.*[67]	1984	0·3	93	52 (56)	3 (3)	—	—
Schwartz *et al.*[68]	1985	0·3	30	16 (53)	—	3 (10)	—
Shepard *et al.*[69]	1985	0·3	62	—	11 (18)	—	—
Balch and Urist[70]	1986	0·3	110	—	—	—	—
Total			433	89 of 185 (48·1)	35 of 267 (13·1)	7 of 118 (5·9)	2 of 41 (5)
Randomized studies							
Chang *et al.*[50]	1987	0·3	24	5 (21)	4 (17)	3 (13)	5 (21)
Kemeny *et al.*[3]	1987	0·3	48	4 (8)	8 (17)	1 (2)	4 (8)
Hohn *et al*[51]	1989	0·2–0·3	67	7 (10)	0 (0)	0 (0)	5 (7)
Martin *et al*[52]	1990	0·3	33	4 (12)	—	—	1 (3)
Wagman *et al.*[71]	1990	0·1–0·3	40	—	0 (0)	—	5 (13)
Rougier *et al*[53]	1992	0·3	81	12 (15)	7 (9)	6 (7)	19 (23)
Allen-Mersh *et al.*[47]	1994	0·2	51	1 (2)	0 (0)	—	0 (0)
Total			344	33 of 304 (10·9)	19 of 311 (6·1)	10 of 220 (4·5)	39 of 344 (11·3)
All studies			777	122 of 489 (24·9)	54 of 578 (9·3)	17 of 338 (5·0)	41 of 385 (10·6)

Values in parentheses are percentages. FUDR, floxuridine

greater than 30 per cent all patients suffered from systemic side-effects such as diarrhoea and/or mucositis.

Upper gastrointestinal symptoms and peptic ulcer disease are potentially avoidable complications of HAC. Hohn *et al.*[83] reported no instance of peptic ulcer in 67 patients. The lack of gastroduodenal toxicity was attributed to meticulous hepatic artery dissection, including ligation of the right gastric artery and of all the small branches in the hepatoduodenal and hepatogastric ligaments distal to the point of cannulation. The addition of oral histamine receptor (H_2) blockers may further diminish gastric toxicity.

Hepatobiliary toxicity is the most frequent and serious dose-limiting side-effect of intrahepatic chemotherapy. Most clinical trials have used a 14-day infusion of FUDR 0·3 mg/kg. The dose of FUDR should be modified if there is an increase in serum glutamic oxaloacetic transaminase, bilirubin or, most importantly, alkaline phosphatase level, compared with baseline values[84]. Most studies report a 20–25 per cent increase in bilirubin level, while hepatocellular injury occurs in up to 50 per cent of patients[84]. A comparison of hepatobiliary toxicity in the studies available is difficult because toxicity criteria such as those recommended by the World Health Organization were not consistently used and reported[85]. Histological alterations associated with HAC include pericholangitis with fibrosis, cholestasis, necrosis of bile ducts and damage to the small vessels supplying the bile ducts[86].

The most serious complication of hepatic artery infusion is biliary sclerosis. While not commonly reported in early trials, an incidence of up to 25 per cent has been reported in more recent randomized studies[53]. The optimal strategy to deal with this problem is early detection by means of close monitoring of liver function test results. These may return to normal if the treatment is discontinued promptly at the first sign of hepatotoxicity, as early stages of biliary sclerosis appear often to be reversible. However, despite early intervention, some patients progress to permanent bile duct stricture. The main stricture is usually located around the main hepatic duct bifurcation but multiple intrahepatic strictures are also almost always present. Since there is often no bile duct dilatation, the diagnosis is made by endoscopic retrograde cholangiography. CT should also be performed to rule out extrinsic bile duct compression from tumour recurrence in the porta hepatis. The pathophysiology of biliary sclerosis is not well understood and may be multifactorial. Changes in the bile ducts include necrosis of the main hepatic duct, and inflammatory and atrophic changes, as well as an end arteritis of the arteries to the bile ducts[87]. These findings suggest that both ischaemia and cytotoxicity contribute to bile duct injury, a complication which has become less common since the addition of dexamethasone to the chemotherapy regimen. Biliary sclerosis can be reversible if identified early and hepatic artery dexamethasone infusion is administered[47].

In the past, HAC has been associated with chemical cholecystitis in up to 32 per cent of patients[62]. This complication is no longer observed since cholecystectomy is now performed routinely at the time of pump/port implantation. Ileitis and small bowel obstruction have also been reported as side-effects of HAC, possibly as a result of shunting of FUDR through the liver or arteriovenous shunting through the tumour bed into the systemic circulation[88].

Randomized trials

Randomized trials of HAC are summarized in *Table 3*. In the 1970s, HAC trials were conducted via external pumps. An early prospective randomized study comparing HAC via ports and external pumps *versus* systemic treatment for colorectal hepatic metastases was conducted by the

Table 3 Randomized studies of hepatic artery chemotherapy for irresectable hepatic colorectal metastases

			Drug (mg per kg per day)		Response rate (%)			Median survival (months)		
Reference	Year	No. of patients	Systemic	HAC	Systemic	HAC	*P*	Systemic	HAC	*P*
Grage *et al.*[89]	1979	61	5-FU (12)	5-FU (20)	23	34	n.s.	13	10	n.s.
Kemeny *et al.*[3]	1987	162	FUDR (0·125)	FUDR (0·3)	20	50	0·001	12	17	n.s.
Chang *et al.*[50]	1987	64	FUDR (0·125)	FUDR (0·3)	17	62	0·003	15	22	n.s.#
Hohn *et al.*[51]	1989	143	FUDR (0·075)	FUDR (0·3)	10	42	0·0001	16	17	n.s.
Martin *et al.*[52]	1990	69	5-FU (500)†	FUDR (0·3)	21	48	0·02	11	13	n.s.
Rougier *et al.*[53]	1992	163	5-FU (500)†‡	FUDR (0·3)	9	43	—	11	15	0·03
Allen-Mersh *et al.*[47]	1994	100	§	FUDR (0·2)	—	—	—	8	15	0·03

†Mg/m^2 ‡Only half of patients received chemotherapy; §less than 25 per cent of patients received systemic chemotherapy. HAC, hepatic artery chemotherapy; 5-FU, 5-fluorouracil; FUDR, floxuridine, n.s., not significant. #$P < 0·03$ if patients with positive portal lymph nodes are excluded

Central Oncology Group[89]. 5-FU was given via the hepatic artery continuously at a dose of 20 mg per kg per day for 14 days followed by 10 mg per kg per day for 7 days and compared with intravenous 5-FU at a dose of 12 mg per kg per day for 4 days followed by 6 mg per kg per day for 4 days. Patients who underwent HAC had many more systemic side-effects, such as nausea, vomiting and diarrhoea, reflecting difficulties associated with the surgical technique and poor hepatic extraction of 5-FU; no definite benefit in survival or response rate was noted, but the criteria for progression and response were relatively loose and might not have correlated with disease status.

Six other randomized trials of HAC have been reported comparing sustained release of FUDR via implantable pumps with systemic 5-FU or FUDR for irresectable hepatic colorectal metastases. In these trials, hepatic arterial FUDR was delivered continuously for 2 weeks in 28-day cycles. These studies showed a greater response rate (more than twofold higher), determined by imaging and/or serum markers, to HAC than to systemic chemotherapy. In all six studies, HAC was associated with a longer median survival than systemic therapy, but the difference was significant in only two studies[47,53]. The study by Allen-Mersh *et al.*[47] was unique in that it demonstrated a significant improvement in quality of life in patients receiving pump chemotherapy compared with controls.

Problems with study designs preclude definitive conclusions regarding the benefit of HAC. In addition, the differences between studies do not allow a valid comparison. In two studies, patients in whom systemic chemotherapy failed crossed over to the hepatic artery infusion arm[3,51]. In four studies, patients with extrahepatic disease were included in one or both arms[3,50–52]. In the two reports describing survival benefit for hepatic artery infusion, patients in the control arm either received no treatment or the treatment was left to the discretion of the primary physician[53]. In none of the studies was the current standard systemic chemotherapy for metastatic colorectal cancer (i.e. 5-FU plus leucovorin) used in the systemic treatment arm[18].

Given the consistent improvement in median survival in all studies using infusion by pump, a significant survival benefit between a group of patients receiving HAC *versus* a group having conventional systemic chemotherapy could be established in a properly designed randomized trial. As previously discussed, HAC should demonstrate a survival advantage over the approximate 12 months' median survival following systemic chemotherapy allowing use of one-tailed statistical analysis (*Table 3*). Accepting a 5 per cent type I (α) error, a 15 per cent improvement in survival rate could be detected by a study containing 144 patients in each arm, with a power of 90 per cent[90]. A similar study design by Moertel *et al.*[14] compared observation, levamisole, and levamisole plus 5-FU in patients with Dukes C colonic cancer and showed an unequivocal 16 per cent increase in survival rate after 3·5 years by including approximately 300 patients in each arm.

Hepatic dearterialization and embolization

Various techniques have been developed to induce ischaemic necrosis of hepatic colorectal metastases. Early studies reporting hepatic artery ligation with or without systemic regional chemotherapy described small numbers of patients with a median survival of 7–14 months[91–93]. Petrelli and colleagues[94] reported a median survival of 10 months in 97 patients treated by hepatic artery ligation without chemotherapy. Hunt and co-workers[41] evaluated hepatic artery embolization in a randomized study of 61 patients with hepatic colorectal metastases. Systemic treatment was compared with embolization with collagen and lyophilized dura, and chemoembolization with starch microspheres and 5-FU repeated monthly via a subcutaneous chamber connected to the hepatic artery. The median survival times were no different between the three groups (8, 7 and 11 months respectively). A recent randomized study compared temporary dearterialization of the liver in association with portal vein 5-FU infusion against no treatment in 54 patients[95]. Temporary dearterialization was performed using a sling around the hepatic artery for 16 h for 5–8 days and intraportal chemotherapy was given for 10 days starting 2 days before occlusion. Further chemotherapy was then repeated every 6 weeks for 2 years in the absence of arterial occlusion. Median survival was significantly better in the treatment arm (17 months) compared with no treatment (8 months). The authors hypothesized that ischaemia sensitized hepatic colorectal metastases to intraportal 5-FU. However, no control arm with chemotherapy alone was included.

Current experience with ischaemic treatment of colorectal metastases is limited and a significant response rate is noted only in association with chemotherapy. The major limitation of this type of treatment is the high rate of hepatic artery thrombosis precluding further therapy[41] and the uncertain efficacy of the approach.

Recent advances in hepatic artery chemotherapy

Recent phase I–II trials have explored combination chemotherapy with infusion pumps. In an attempt to increase the effectiveness of hepatic artery infusion, Kemeny *et al.*[75] recently combined FUDR and leucovorin in a dose escalation study. The addition of leucovorin 15 mg per m^2 per day to FUDR 0·3 mg per kg per day resulted in an improved response rate (partial and complete response rate 75 per cent) compared with previous studies using FUDR alone. With reduction of toxicity as another important goal of new trials, dexamethasone was added to FUDR and leucovorin resulting in a rate of biliary sclerosis of 3 per cent and a response rate of 78 per cent[76]. This represented a definite improvement over previous regimens.

Arisawa *et al.*[96] investigated the effect of the addition of dexamethasone on the growth of colorectal hepatic metastases in an animal model and its effect on colonic cancer cells *in vitro*. While dexamethasone did not show any cytotoxic effect on cultured cells *in vitro*, *in vivo* studies showed improved survival with hepatic infusion of dexamethasone alone compared with that of untreated control rats with hepatic colorectal metastases. In the same study, the inhibition by dexamethasone of tumour-induced angiogenesis in subcutaneously implanted colorectal cancer cells suggested that the angiostatic effect of dexamethasone may contribute to the increase in response rate when it is administered with FUDR.

One limitation of HAC is the high rate of extrahepatic disease progression reported in up to 56 per cent[3] of patients so treated. Stagg and colleagues[97] reported a phase II trial combining FUDR 0·1 mg per kg per day by intrahepatic arterial infusion for 8 days with 5-FU 15 mg/kg given as a bolus injection via the side port of the pump once a week for 3 weeks with the cycle being repeated every 35 days. A major response was observed in the liver in 50 per cent of patients, while extrahepatic progression occurred in only 22 per cent of patients, suggesting a systemic benefit from the incomplete extraction of 5-FU in the liver. No patient had treatment interrupted because of drug toxicity. Most side-port bolus injections of 5-FU were given by local physicians. A combined approach directed at both hepatic and extrahepatic disease may ultimately be the optimal strategy for these patients.

A new potential strategy in regional chemotherapy is the application of chronobiological modification of intrahepatic FUDR infusion. It has been demonstrated in animal models that circadian patterns of both intra-arterial and intravenous FUDR infusion may change the toxicity dramatically[98]. In a rat model of metastatic colorectal cancer, circadian hepatic arterial FUDR infusion achieved a 90 per cent complete response rate without toxicity or death, while the mortality rate for continuous delivery of FUDR via the hepatic artery over 24 h was 80 per cent[99]. In a retrospective study of 50 patients at the University of Minnesota, those receiving circadian infusion of FUDR tolerated a larger dose (0·79 mg per kg per day) with less hepatic toxicity compared with those receiving a standard constant infusion[100]. The circadian modification in this study delivered 68 per cent of the FUDR between 15.00 and 21.00 hours, 2 per cent between 03.00 and 09.00 hours, and 15 per cent in the adjacent intervals. The combination of 5-FU and leucovorin as systemic treatment of metastatic colorectal cancer has been given by a 14-day circadian intravenous infusion in another phase I–II trial, with promising result[101]. Further prospective randomized trials will be necessary to test the effect of circadian modification on HAC.

In an attempt to increase further the dose intensity of chemotherapy delivered by the hepatic arterial route, the group at Yale[102] performed high-dose HAC with subsequent detoxification of hepatic venous blood. This was achieved by simultaneous placement of a double-balloon catheter in the inferior vena cava and a hepatic artery catheter percutaneously. Chemotherapeutic agents were infused via the hepatic artery and the hepatic venous effluent was circulated through an extracorporeal circuit containing chemotherapy filtering agents. The 5-FU dose was increased to 1000–5000 mg per m^2 per infusion, and doxorubicin to 50–120 mg/m^2. The treatments were relatively well tolerated with transient hypotension and leucopenia emerging as the major toxic side-effects. While the number of patients was too small to comment on therapeutic efficacy, this method of dose escalation proved feasible. It is unclear whether this technically sophisticated technique offers any advantage over more traditional prolonged infusions, as duration of infusion may be an important variable. Further studies are needed.

Combined approaches

At present there is renewed interest in testing HAC infusion as adjuvant chemotherapy after resection of colorectal hepatic metastases. Sugihara *et al.*[103] reported that 64 of 109 patients having curative hepatic resection of colorectal metastases developed recurrence during a median follow-up of 35 months. Among 72 sites of recurrence, 34 were in the liver, 20 in the lung, 12 in the abdominal cavity and six elsewhere. A prospective randomized study in a small number of patients has shown that resection plus HAC displayed a trend to improved survival compared with resection alone, especially for multiple resectable lesions[104]. Curley and colleagues[39] treated 20 patients with intrahepatic boluses of 5-FU 15 mg/kg at intervals of 1 week for 6 months. Nine of 18 evaluable patients developed recurrence: three in the liver and six at extrahepatic sites. Based on these results, several randomized trials of intra-arterial hepatic FUDR as adjuvant therapy after curative resection of hepatic metastases are being conducted with the major cooperative groups. Another interesting novel approach is the combination of HAC with cryosurgery in an attempt to cytoreduce liver disease before implantation of arterial ports or pumps[38]. This approach is conceptually similar to cytoreductive surgery for ovarian and peritoneal malignancies before chemotherapy.

Conclusion

HAC appears to be the most successful method of limiting tumour growth in patients with hepatic colorectal metastases; the systemic side-effects are minimized compared with those associated with systemic intravenous chemotherapy. Implantable continuous infusion delivery systems carry the lowest risk of permanent loss of hepatic artery access (5 per cent), are most convenient for patients and, when managed appropriately, are well tolerated. Regimens containing dexamethasone may reduce biliary toxicity.

Despite this progress, the general application of HAC still awaits clear demonstration of its benefits in well designed phase III randomized studies. Data do not as yet support the use of hepatic artery infusion outside investigational studies and the technique should be restricted to specialized centres. Unfortunately, most randomized studies have compared HAC with suboptimal systemic chemotherapy. The roles of continuous hepatic artery infusion and systemic chemotherapy may evolve through parallel methods of investigation. The excellent local response along with the high rate of systemic failure with hepatic artery infusion alone suggests that HAC will remain an attractive regional approach to metastatic colorectal cancer. Future trials should address both hepatic tumour control and systemic risks of failure.

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Review

Liver metastases from colorectal cancer: lessons from past and present clinical studies

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In patients with primary colorectal cancer the development of liver metastases has traditionally been equated with imminent demise. This metastatic event is remarkably common; indeed, liver metastases are present in some 25 per cent of patients at the time of initial colorectal resection and over 50 per cent of patients will eventually develop them. Some 90 per cent of patients who die from colorectal cancer have liver metastases. There are few cancers in which the metastatic pattern has such a high degree of predictability. Information from past and present clinical studies should, therefore, provide a basis for logical approaches to prevention and treatment.

More than 50 per cent of patients with primary colorectal cancer develop liver metastases[1]. Spread of malignant cells from primary colorectal cancer to the liver occurs via portal venous drainage. Subsequent growth and nutrition is dependent upon an arterial blood supply[2]. The mechanism by which cancer cells reach the liver is complicated. Initially they must detach themselves from the primary colorectal cancer, migrate through the basement membranes and extracellular matrix, travel unhindered within the portal venous circulation, reach the liver in an active and unharmed state, and reattach themselves to liver parenchyma[3,4]. If they are to grow and develop they must take on the characteristics of a micrometastasis and hence stimulate the development of a neovascular blood supply (angiogenesis)[5]. This is a sophisticated process and much can go wrong. It is inconceivable that every malignant cell entering the portal circulation will successfully develop into a micrometastasis. Indeed, in animal models utilizing portal vein injection of malignant cells, the liver is demonstrated to be a very effective 'trapper' of malignant cells as 'the organ of first encounter' but is comparatively inhospitable to subsequent metastatic development[6,7]. Animal liver metastases will only develop if more than 10^6 malignant cells are injected into the portal venous system. Once trapped, however, the malignant cells fail to recirculate and subsequent metastases (e.g. to the lungs) only develop from liver metastases[8]. In other words, it is likely that extrahepatic metastases arise from liver metastases. This pattern is recognized in the clinical situation where extrahepatic metastases are rare in the absence of synchronous liver metastases. In animal models any form of trauma to the liver, either before or soon after tumour cell injection, increases the incidence of liver metastasis both at the site of injury and in lobes distant from the site of local trauma[9].

There is much evidence to suggest that in most, if not all, patients with primary colorectal cancer, micrometastases exist in the liver in a dormant state[10,11]. It is probable that only a very small proportion of micrometastases develop into clinically overt disease; although trapped in the liver they are presumably prevented from growing owing to failure of mechanisms that determine metastatic growth. In this regard it is the development of a neovascular circulation that appears to be of major importance[12]. The change from portal venous to hepatic arterial perfusion is responsible for changes in hepatic haemodynamics which are becoming increasingly recognized. Blood vessels in established liver metastases have abnormalities in neuropeptide innervation and an incomplete, or indeed absent, smooth muscle coat[13]. This explains why the introduction of vasoconstrictor drugs, such as angiotensin II, into the hepatic artery reduces blood flow to normal liver by vasoconstriction and so diverts flow to tumours whose blood vessels are unable to constrict[14]. Recent studies have also suggested that negative regulators of angiogenesis, possibly arising from the primary tumour itself, determine whether metastases have the ability to grow[5].

Clinical studies have also revealed a change in distribution between arterial and portal venous flow, recognized by hepatic flow scintigraphy with sulphur colloid. A hepatic perfusion index is derived which correlates with the subsequent development of liver metastases[15]. More recently duplex ultrasonography has been used to measure hepatic arterial and portal venous flow in patients with colorectal cancer[16]. The Doppler perfusion index (DPI) is higher in patients with liver metastases present at the time of colorectal resection or in those who develop them during the following year[17,18]. The sensitivity of DPI for liver metastases is 100 per cent with a predictive accuracy of 86 per cent, providing further evidence for occult liver metastases influencing long-term prognosis[18]. Studies using other complex hepatic imaging techniques, such as sequential computed tomography[19] and technetium-99m macroaggregated albumin injections[20], have provided additional confirmatory evidence for the existence and prognostic significance of occult liver metastases.

Attempts have been made to use simpler clinical parameters to predict which patients will subsequently develop liver metastases. For example, in one prospective study patients without detectable colorectal liver metastases (either clinically or by imaging) were followed for up to 10 years and regular scanning of the liver

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performed. A clinical prognostic index was derived to determine which factors correlated with the subsequent development of liver metastases. The most sensitive parameters were Dukes C disease and a change in serum alkaline phosphatase at the time of initial colorectal resection[21].

Patients with Dukes C disease have metastases in adjacent lymph nodes and, therefore, have clones of malignant cells with the ability to spread via the lymphatic system into adjacent lymph nodes and grow. It would seem reasonable that these same tumours have malignant cells which are more likely to enter and grow in the liver and develop into overt metastases. Lymph node metastases may well represent a marker of malignant potential indicating a greater likelihood for development of overt hepatic metastases.

Hypothesis

The following hypothesis is proposed. In all patients with primary colorectal cancer malignant cells enter the portal venous system and are trapped within the liver. Although the liver is an effective trapper, it is relatively refractory to metastatic growth; however, some micrometastases eventually develop into overt metastases. Although multiple factors determine which malignant cells grow, the development of a neovasculature is important. However, it is likely that specific characteristics of the malignant cells themselves will determine their propensity to develop into metastases. If it were possible to recognize which patients possess potentially malignant micrometastases, this would influence the decision with regard to adjuvant therapy. If this hypothesis is valid for determining a therapeutic strategy then confirmatory evidence should be available from existing clinical studies.

Evidence from clinical studies

Adjuvant chemotherapy

Let us first consider the available data from randomized prospective trials on adjuvant systemic chemotherapy in patients with primary colorectal cancer. Since the liver is considered to contain occult metastases that are more likely to become overt in patients with Dukes C disease than in those with Dukes B lesions, any benefits for systemic chemotherapy following 'curative' resection of colorectal cancer should be greater for Dukes C disease, with minimum advantage for Dukes B disease. In addition, any survival benefit should correspond with a reduced incidence of metachronous liver metastases. Is this so? Undoubtedly yes.

In 1988[22] a meta-analysis of randomized adjuvant studies using systemic 5-fluorouracil (5-FU) for up to 1 year demonstrated a marginal overall reduction in the odds ratio of death of approximately 17 per cent ($P = 0·03$) and an absolute 5-year survival benefit of 3·4 (95 per cent c.i. 1·2–8) per cent. However, in recent years there have been more impressive reports. These have resulted from combination chemotherapy (5-FU, vincristine and lomustine methyl CCNU)[23], by combining 5-FU with immunomodulatory drugs such as levamisole[24] or by biomodulating 5-FU with leucovorin[25]. In the Intergroup study, for example, 352 patients with Dukes B_2 and 971 patients with Dukes C disease were randomized to surgery alone or surgery with 5-FU and levamisole for 1 year[24]. In patients with Dukes C disease there was a significant reduction of 41 per cent in the risk of cancer recurrence (chiefly within the liver) and a corresponding reduction in mortality of 33 per cent. This initial improvement corresponded with an absolute survival benefit of approximately 5 per cent which was maintained at 5 years. The survival benefit for patients with B_2 disease did not reach conventional levels of significance and there was no reduction in the incidence of liver metastases.

Three cooperative groups evaluated 5-FU and leucovorin individually but because their protocols were so similar their data was pooled to allow a combined analysis[26]. Patients with Dukes B and C disease were randomized to surgery alone or surgery followed by 5-FU and leucovorin administered for 5 days every 28 days for 6 months. The crude rate of recurrence in the liver was twice as high in the control group compared with the treatment group. Overall, the chemotherapy group had significantly lower rates of an adverse event (35 per cent lower) and death (22 per cent lower) than the control group. However, the 3-year overall survival rate for patients with Dukes B disease was not significantly different between the control and chemotherapy groups. There was a statistically significant improvement in overall survival only in patients with Dukes C lesions (hazard ratio for overall survival 0·7 (95 per cent c.i. 0·53–0·92)). Accordingly there is now considerable evidence of a survival benefit for systemic chemotherapy in patients with Dukes C disease, but considerable uncertainty of benefit for those with Dukes B lesions. This survival improvement correlates with a similar reduction in the incidence of liver relapse in the first 2–3 years following colorectal resection.

If hepatic micrometastases exist, it could be argued that the incidence of overt liver metastases might be reduced by selectively delivering high-dose chemotherapy to the liver through the portal venous system. Any effect on inhibition of occult micrometastases should be associated with an improvement in survival. Any benefit, however, would more likely be demonstrated in patients with Dukes C disease.

This hypothesis has been tested in ten published studies of adjuvant cytotoxic portal vein infusion in primary colorectal cancer. Portal vein cytotoxic infusion is usually commenced at operation or in the immediate postoperative period, and given continuously for the first 7 days after surgery. This short perioperative therapy is in marked contrast to long-term chemotherapy when 5-FU is given systemically for 6 months; toxicity is reduced as, indeed, is cost. An original hypothesis-generating trial demonstrated a significant reduction in the incidence of liver metastases with survival benefit[27]. Nine subsequent trials have demonstrated improvement to a lesser extent. For example, a Swiss group[28] has recently reported a 25 per cent incidence of relapse confined to the liver in the control arm compared with 12 per cent in the portal vein infusion group in node-positive patients. Overall, portal vein infusion reduced the risk of recurrence by 21 per cent (hazard ratio 0·9 (95 per cent c.i. 0·62–1·00); $P = 0·051$) and the risk of death by 26 per cent (0·74 (95 per cent c.i. 0·57–0·97); $P = 0·026$). The major risk reduction was in patients with Dukes C disease as, indeed, was the overall absolute survival improvement.

A meta-analysis of all ten published trials of portal vein cytotoxic infusion, including a total of 3499 patients, has provided confirmatory evidence[29]. Overall, portal vein infusion was associated with a mean(s.d.) 18(6) per cent reduction in the annual risk of death from any cause with a 20(6) per cent reduction in death from colorectal cancer. Interestingly in this meta-analysis, overall survival diverged significantly at 2 years and at 5 years was 64 per cent in the portal vein infusion group *versus* 59 per cent in the surgery-only group. The benefit was significantly greater for patients with Dukes C disease (54·2 per cent *versus* 46·6 per cent) than for those with Dukes B lesions (76·3 per cent *versus* 72·1 per cent).

It is well known that over 90 per cent of patients developing colorectal liver metastases do so within 2 years of primary surgery. The observation that significant benefits from portal vein infusion occur after 2 years is consistent with an effect on the natural history of occult liver metastases. A diminution in their rate of growth and development into overt metastases would have overall survival benefits only after approximately 2 years.

The published results of both adjuvant systemic chemotherapy for 6–12 months and portal vein infusion for 1 week are roughly comparable, with an approximate 5 per cent improvement in absolute survival at 3 years. The major benefits from both treatments occur in patients with lymph node-positive disease. This is entirely consistent with the hypothesis that chemotherapy inhibits occult hepatic micrometastases rather than producing systemic effects outside the liver. Subsequent relapse in extrahepatic organs is also inhibited, since extrahepatic metastases spread from liver metastases.

There is now sufficient evidence to recommend that patients with Dukes C disease who are otherwise sufficiently fit should receive adjuvant cytotoxic chemotherapy. There is still significant uncertainty, however, with regard to the benefits for patients with Dukes B lesions. Randomized trials in patients with Dukes B disease should therefore include a surgery-only arm.

Liver resection

Additional support for the hypothesis can be found by a critique of the reported data on liver resection for localized metastatic disease. Conceptually it seems illogical that resection of solitary or localized metastatic disease within the liver should have a favourable effect on survival. However, in the absence of prospective randomized trials, carefully documented prospective studies and clinical audit report median 3- and 5-year survival rates of 40 per cent and 25 per cent respectively[30]. These survival data following resection of liver metastases are similar to what would be expected in patients who undergo primary colorectal resection of Dukes C disease. It would appear that resection of localized liver metastases downstages Dukes 'D' to Dukes C disease.

As mentioned previously, the majority of micrometastases that exist within the liver remain dormant and presumably never develop into overt metastatic disease. Metachronous overt liver metastases become clinically apparent within 2 years of colorectal resection. Other metastases within the liver should have appeared by that time and the fact that they are still dormant indicates that they are unlikely to develop into overt liver metastases. Interestingly, this is supported by the observation that resection of metachronous metastases is associated with improved survival compared with resection of synchronous metastases. This suggests that patients with synchronous metastases have more aggressive tumours, which have grown at the same rate as the primary tumour and which are less likely to benefit from resection than a metachronous tumour of slower growth rate. This is supported by the reported independent prognostic variables that influence 3- and 5-year survival rates following liver resection. These are the degree of differentiation of the primary tumour, whether the adjacent lymph nodes are involved, and whether the tumour is synchronous or metachronous[30,31].

There is, therefore, an argument for adjuvant systemic chemotherapy following liver resection, particularly if one considers that the disease may be downstaged by surgery from a Dukes 'D' to a Dukes C equivalent which, as mentioned previously, is an indication for adjuvant systemic chemotherapy. In addition, approximately 50 per cent of patients who relapse after liver surgery do so with extrahepatic metastases. A randomized trial comparing liver resection with liver resection and systemic chemotherapy is being undertaken under the auspices of the European Organisation for Research and Treatment of Cancer (EORTC).

Hepatic arterial infusion

There is additional information available from studies utilizing hepatic arterial cytotoxic infusion for established multiple liver metastases. Patients with multiple metastases unsuitable for resection might be eligible for treatment by means of intrahepatic arterial chemotherapy. Numerous studies have shown that this approach achieves a higher locoregional control rate than systemic chemotherapy, although few studies have demonstrated an overall improvement in survival[32]. This is to be expected. Even if multiple liver metastases respond to high-dose locoregional chemotherapy, this is unlikely to affect the development of extrahepatic metastases, if such lesions develop from liver metastases. Once again, the characteristics of the primary tumour and the length of time from resection of the primary lesion to the development of liver metastases appear to determine the response rate[33,34]. The combination of locoregional cytotoxic chemotherapy with systemic chemotherapy is more likely to yield favourable survival rates and preliminary studies support this[35].

Conclusions

Liver metastases represent a major determinant of outcome following apparently successful curative colorectal resection. The majority of patients have hepatic micrometastases which remain dormant, but undoubtedly a proportion develop the necessary mechanisms for growth and stimulation of a neovascular circulation.

Patients with Dukes C disease have a greater propensity for development of liver metastases and it is this group of patients who benefit most from adjuvant systemic chemotherapy. There are few reasons for not offering patients with Dukes C disease (provided that they are fit enough) adjuvant cytotoxic chemotherapy. Presently available data suggest that the benefits from 6 months of treatment with 5-FU and levamisole or folinic acid are equivalent to those of a 1-week portal vein infusion with 5-FU, although the combination of the two could be additive. Patients with Dukes C disease should be considered for randomization into the QUASAR ('quick and simple and reliable') study in which high- and low-dose 5-FU and folinic acid are being compared with high- and low-dose 5-FU and levamisole. This trial is accruing patients at a rapid rate. The situation in patients with Dukes B lesions is less certain since they are less likely to have hepatic micrometastases and are thus less likely to benefit. Accordingly, such patients should be offered the opportunity of randomization into a trial such as the QUASAR study, with a surgery-only arm. Because of the natural history of hepatic micrometastases and because the majority of overt metastases develop within 2 years, such adjuvant trials are unlikely to demonstrate significant benefits in overall survival within 2 years of surgery.

In patients with localized colorectal liver metastases, liver resection probably downstages Dukes 'D' to Dukes C disease and so such patients should be considered for adjuvant systemic chemotherapy by randomization into the ongoing EORTC study of liver resection alone *versus* liver resection plus systemic chemotherapy. In patients with multiple liver metastases locoregional chemotherapy has a higher response rate than systemic chemotherapy. However, there is evidence that this should be combined with systemic treatment. A randomized trial, under the auspices of the Medical Research Council in the UK, is comparing locoregional chemotherapy with systemic chemotherapy and appropriate patients should be considered for inclusion within this study. Data from adjuvant trials, as well as studies involving the metastatic process and haemodynamic changes, should be utilized when determining a logical strategy for treating patients with resected colorectal cancer.

It is recognized that all these strategies are of little value if the primary cancer surgery is not performed to the highest standard. Surgeons are aware of their responsibility in this regard to ensure a low locoregional recurrence rate. Only when this is satisfactorily achieved will the benefits of any additional therapy be apparent.

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Announcement

European Surgical Fellowships

Council of The British Journal of Surgery Society is pleased to announce the availability of the first tranche of European Surgical Fellowships for 1996.

Each Fellowship will have a value of up to £3000 and is intended to allow surgeons working in the United Kingdom to visit centres in other European countries, or surgeons working in other European countries to visit the United Kingdom. Applicants must be under 40 years of age and should submit details of their proposed itinerary, its anticipated cost, a copy of their curriculum vitae and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

Applications should be sent to Mr J. R. C. Sainsbury, Company Secretary, The British Journal of Surgery Society, Department of Surgery, The Royal Infirmary, Lindley, Huddersfield HD3 3EA, UK by 28 June 1996.

J. R. C. Sainsbury

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Review

Role of endoscopic injection therapy in the treatment of bleeding peptic ulcer

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Of patients with peptic ulceration who are actively bleeding at endoscopy, 80 per cent will continue to bleed or rebleed in hospital; 50 per cent of those who have a non-bleeding visible vessel will also rebleed. Endoscopic injection treatment stops active bleeding and prevents further haemorrhage in most of these patients. The mechanism of action may include tamponade, vasoconstriction, sclerosis, tissue dehydration and thrombogenesis; substances injected include adrenaline, sclerosants, alcohol, thrombin, or a combination of agents. Although trials often define the need for surgery as an injection treatment failure, an alternative view is that endoscopic control may facilitate safe, early, elective surgery. A successful outcome may require a combination of endoscopic and operative approaches.

In specialized centres the mortality rate from peptic ulcer haemorrhage has been greatly reduced and is now between 2 and 6 per cent[1–4]. It is difficult to define a single factor responsible for this low mortality rate; it is possible that further reductions will not occur, since ulcer bleeding is an agonal event in some terminally ill patients and occurs in the very frail elderly who have severe co-morbid diseases. In this review we consider the role of endoscopic injection therapy for bleeding peptic ulcer.

A range of endoscopic therapies has been shown to stop bleeding and to reduce the risk of further haemorrhage (*Table 1*). These include thermal modalities such as argon[5–7] or neodymium yttrium–aluminium–garnet (NdYAG)[8–18] laser, electrocoagulation using monopolar[19–21] or multipolar[22–28] probes, and the heater probe[29–31]. Much interest has focused recently on injection therapy, which requires no expensive equipment and is within the capability of most experienced gastrointestinal endoscopists. Many clinical trials have shown that injection therapy improves the prognosis of patients who require hospital admission for bleeding ulcer, but several important questions remain.

Table 1 Endoscopic treatment for bleeding ulcer

- Thermal
  - Argon laser
  - Neodymium yttrium–aluminium–garnet laser
  - Heater probe
  - Electrocoagulation
- Injection
  - Adrenaline
  - Sclerosants
  - Alcohol
  - Thrombin
- Other
  - Topical sprays
  - Microwave coagulation
  - Mechanical

Which patients should be treated by injection therapy?

Eighty per cent of peptic ulcer bleeds stop spontaneously[32,33], and endoscopic or surgical intervention is unnecessary in this group. Factors associated with uncontrolled bleeding and death include age over 60 years, shock at the time of presentation and a haemoglobin concentration of less than 10 g/dl. The presence of co-morbid disease increases the risk of postoperative complications[34–37]. The most important predictive information is found at endoscopy (*Fig. 1*); 80 per cent of patients actively bleeding during the examination will continue to bleed or rebleed in hospital and 50 per cent of those who have a non-bleeding visible vessel will also rebleed[38–44]. Endoscopic therapy stops active bleeding and prevents further haemorrhage in most

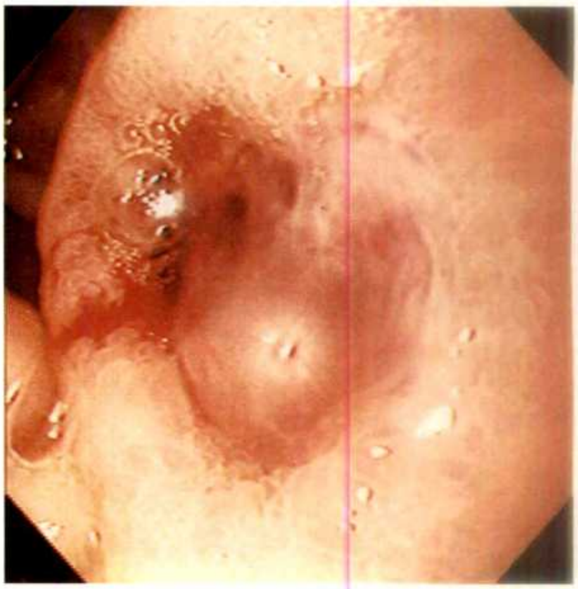

Fig. 1 Endoscopic view of a duodenal ulcer containing a 'visible vessel'

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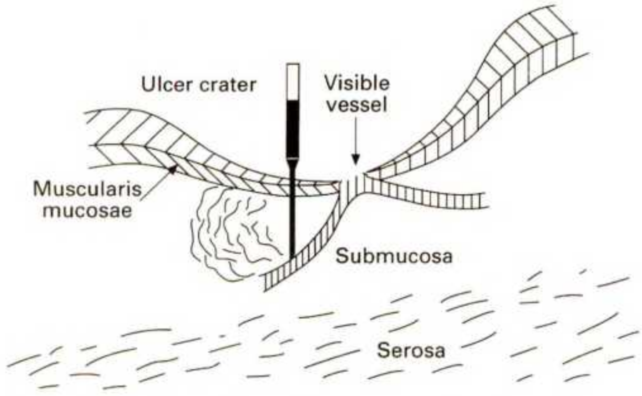

Fig. 2 Injection treatment of bleeding peptic ulcer. The ulcer bleed is due to erosion of a major submucosal artery and disruption of the muscularis mucosae; the serosa is rarely involved. Injection is usually directed beside the visible vessel to induce tamponade, vasoconstriction or sclerosis of the vessel

of these patients and surgery may be reserved for the failures of endoscopic management. In contrast, a clean ulcer base is not associated with further bleeding and endoscopic therapy is unnecessary.

How does endoscopic therapy work?

It is not clear how injection therapy stops active bleeding and prevents rebleeding (*Fig. 2*). This is because tissue specimens following injection are rarely available and also because it is difficult to differentiate between the histological effects of treatment and those of a chronic ulcer. Inflammation, vasculitis and thrombosis of vessels are inherent features of peptic ulceration, and an appropriate reproducible animal model of bleeding peptic ulcer is not available.

The efficacy of injection therapy may be due to one or all of the following mechanisms.

Tamponade

Injection of fluid into a fibrotic rigid ulcer causes compression of the bleeding vessel. This hypothesis is supported by the trial reported by Lin *et al.*[45], in which injection of saline or dilute dextrose into bleeding ulcers was more effective than conservative therapy in stopping bleeding and had a similar efficacy to injection of absolute alcohol. A similar conclusion was reported by Fleig[46], who showed that endoscopic injection of water stopped bleeding and prevented ulcer rebleeding. In animal models of gastrointestinal bleeding it is not possible to show that haemostasis can be achieved by injection of inert fluids[47,48]; these models do not involve chronic ulceration and fibrosis, limiting any tamponade effect. Although there are reservations about the importance of this mechanism, it may at least contribute to the efficacy of injection therapy. Larger clinical trials are needed to examine the effect of injection therapy using inert fluids.

Vasoconstriction

Dilute adrenaline stops active bleeding both in models of gastrointestinal bleeding[47,48] and in clinical practice[49,50]. This is assumed to be due to vasoconstriction of the bleeding artery, although atheromatous change in the vessel, perivascular fibrosis and inflammation may reduce the capacity of the artery to constrict. Most endoscopists inject relatively large volumes of dilute adrenaline (5–20 ml) and tamponade may also be significant. Blanching around the injected area occurs at the time of adrenaline injection; the gastric mucosa of dogs had a 'cyanotic' appearance when injected with dilute adrenaline[48]. In these animal experiments histological examination showed that inflammation is completely localized to the injected area, and that necrosis and vascular changes rarely occur after injection of adrenaline.

In clinical trials dilute adrenaline injections not only stop active bleeding, but also largely prevent rebleeding[51,52], suggesting that adrenaline may thrombose the bleeding artery. This is likely to be a simple consequence of vasoconstriction, but adrenaline-induced alteration of platelet function[53,54] and stimulation of the coagulation cascade may also be a factor.

Sclerosis

Polidocanol, ethanolamine and sodium tetradecyl sulphate are widely used sclerosants. When injected into the gastric mucosa of dogs, differing concentrations of polidocanol caused extensive necrosis and deep ulcers in a dose-dependent manner[48,55]. Venous thrombosis invariably follows sclerosant injection but endarteritis and arterial thrombosis occur less often[47,48,55]. Indeed, in a rabbit model of mucosal bleeding, ethanolamine injection was not associated with thrombosis of major arteries and temporarily increased the rate of bleeding. Adrenaline injections on the other hand had prompt haemostatic activity[47]. Sclerosant injections are less effective than thermal methods in stopping experimental active bleeding from the gastric mucosa[47].

A clinical trial has reported that sclerosant injections are useful in stopping active bleeding[56], but most authorities consider that if sclerosants have a role it is likely to be in the prevention of rebleeding rather than in the treatment of active haemorrhage.

Tissue dehydration

Ethanol (98 per cent) injections cause profound dehydration of tissues leading to vigorous inflammation, extensive necrosis and ulcer formation[48,55]. Surrounding areas are congested and hyperaemic; blood vessels are partially thrombosed. In experimental models active bleeding is rarely stopped by alcohol injection, contrasting with the efficacy of adrenaline and laser therapy.

Thrombogenesis

Injection of bovine thrombin initiates the clotting cascade. Several small studies have shown the value of thrombin injection in bleeding peptic ulcers[57–60], but no study has been large enough to allow a comparative assessment of efficacy with other modalities.

Which substances should be injected?

Numerous clinical trials have examined the efficacy of a variety of injected substances and it is difficult to show that any particular regimen is best.

Dilute adrenaline

Chung and co-workers have pioneered the use of dilute adrenaline. In a controlled trial[49], patients who presented with actively bleeding ulcers were randomized to receive endoscopic injection with 1 : 10 000 adrenaline or were managed without endoscopic therapy[49]. Injected patients required significantly less blood transfusion, needed fewer emergency surgical operations and had a shorter hospital stay than non-injected patients. 'Rebleeding' was not reported in this trial and the mortality rate was similar in both groups.

The effective concentration of adrenaline is not known. Chung's group has used a concentration of 1 : 10 000, while the Edinburgh group has favoured a 1:100 000 solution. The results of endoscopic therapy are very similar in trials reported by these two groups[49–51]. Significant and potentially important increases in plasma adrenaline concentrations follow endoscopic injection with 1 : 10 000 adrenaline solutions[61], which could have adverse effects in patients with coexisting cardiac disease. For this reason the present authors favour dilute injections although, in clinical practice, no significant complications have been reported following use of the 1 : 10 000 concentration.

Sclerosants

A range of sclerosing agents have been injected directly into and around bleeding ulcers in an attempt to stop active bleeding and prevent rebleeding. These include polidocanol, 5 per cent ethanolamine and 3 per cent sodium tetradecyl sulphate. Several uncontrolled series[62,63] performed in the early 1980s suggested that injection of these agents was effective and safe. There are no controlled trials in which outcome has been assessed in patients randomized to sclerosants or to conservative (no injection) treatment, but several trials have compared the efficacy of sclerosant injection with other haemostatic methods.

Benedetti *et al.*[57] randomized patients presenting with bleeding from a range of causes to injection with 1 per cent polidocanol or thrombin, and showed similar haemostatic effects for these treatments. Strohm *et al.*[64] randomized patients to one of four treatment arms (fibrin glue, 1 per cent polidocanol, dilute adrenaline or adrenaline plus polidocanol) and showed little advantage for any one approach. Finally, Rutgeerts and colleagues[65] showed that injection of polidocanol is as effective as NdYAG laser photocoagulation therapy in patients with ulcer bleeding.

More studies have examined the effectiveness of adrenaline in combination with sclerosants (*Table 2*). Panes *et al.*[67] randomized matched patients to a combination of 1 : 10 000 adrenaline plus 1 per cent polidocanol or to no injection. Recurrent bleeding occurred in 5·5 per cent of injected patients, compared with 43 per cent of controls ($P < 0{\cdot}001$), with a corresponding reduction in the need for emergency surgery, blood transfusion requirements and duration of hospital stay. Rajgopal and Palmer[66] subsequently showed that the combination of 1 : 100 000 adrenaline plus 5 per cent ethanolamine reduced rebleeding rates in patients who had a range of major endoscopic stigmata. In this study, some control patients were injected when they rebled, most of whom then avoided emergency surgery; this defect in trial design resulted in the loss of possible differences in other endpoints. Moreto *et al.*[70], in a small clinical trial of 38 patients, demonstrated that haemostasis was achieved in most patients treated with a combination of ethanolamine plus thrombin injections; one of 19 treated patients developed uncontrolled bleeding, compared with further bleeding in eight of 19 non-injected controls. The role of the sclerosant in these trials is difficult to define for two reasons: first the trials suffer from the common problem of small sample size and, second, the sclerosant has invariably been injected in combination with another agent of proven therapeutic value.

To try to define the role of the sclerosants three studies have compared outcome in patients randomized to adrenaline injection or to a combination of adrenaline and a sclerosant (*Table 3*). Chung *et al.*[52] randomized actively bleeding patients to injection with 1 : 10 000 adrenaline or to adrenaline followed by 3 per cent sodium tetradecyl sulphate. The groups were well matched in all

Table 2 Controlled trials of adrenaline plus sclerosant *versus* conservative treatment for ulcer bleeding

				Rebleeding or uncontrolled haemorrhage			
Reference	Year	No. randomized	Endoscopic finding	Injection	Control	*P*	Comment
Rajgopal and Palmer[66]	1991	109	Active bleeding (9) Other stigmas (100)	7 of 52	25 of 53	< 0·001	1:100 000 adrenaline plus 5 per cent ethanolamine. Some control patients injected after rebleeding
Panes *et al.*[67]	1987	113	Active bleeding (28) Oozing or clot (46) Non-bleeding visible vessel (39)	3 of 15 0 of 22 8 of 18	10 of 13 14 of 24 15 of 21	< 0·01 < 0·05 < 0·01	1:10 000 adrenaline plus 1 per cent polidocanol. Reduced transfusion need in injected patients
Balanzo *et al.*[68]	1988	72	Various stigmas	7 of 36	15 of 36	< 0·05	1:10 000 adrenaline plus 1 per cent polidocanol. Reduced surgical intervention and transfusion needs in injected group
Oxner *et al*[69]	1992	93	Active bleeding (5) Other stigmas (88)	8 of 48	21 of 45	< 0·05	1:10 000 adrenaline plus 1 per cent polidocanol. Fewer deaths in injected patients (four *versus* nine, *P* not significant)

relevant aspects. Initial haemostasis was achieved in almost all patients; indeed the only failures were those in whom torrential bleeding prevented visualization and injection of the bleeding ulcer. After initial control of bleeding only two patients in each group rebled in hospital. Similar results were obtained by Choudari and Palmer[51], who randomized patients presenting with a range of major endoscopic stigmata to injection with 1 : 100 000 adrenaline or to adrenaline plus an injection of 5 per cent ethanolamine. Permanent haemostasis was achieved in 85 per cent of patients in both groups. Villanueva *et al.*[71] demonstrated a similar outcome after injection with adrenaline plus polidocanol or treatment with adrenaline alone. No study has compared haemostasis with dilute adrenaline with that achieved by injection of a sclerosant alone.

Sclerosant injections may be associated with serious complications. These probably occur as a consequence of extensive thrombosis of arteries serving the upper gastrointestinal tract. Levy and colleagues[72] reported a fatal case of gastric antral necrosis following injection with a combination of adrenaline and sodium tetradecyl sulphate. Similar complications of sclerosant injection have been reported by other authors[73,74]. Luman *et al.*[75] described a common bile duct stricture causing obstructive jaundice after repeated injection of a posterior duodenal ulcer with adrenaline and 5 per cent ethanolamine. Because sclerosants appear to offer no advantage over injection with adrenaline alone, and because of their uncommon but potentially serious side-effects, the present authors do not believe that they should play a role in injection therapy for bleeding ulcers.

Alcohol

The efficacy of 98 per cent ethanol injection has been examined in several clinical trials (*Table 4*). Sugawa *et al.*[79] and Pascu and co-workers[76] reported that absolute alcohol is effective in actively bleeding ulcers. More recently, Lazo *et al.*[77] reported a small study in which patients with non-bleeding visible vessels were treated by injection or acted as non-injected controls. Rebleeding was significantly less common in the injected group. Lin and colleagues[45] reported that alcohol injection stopped active bleeding and prevented rebleeding in 86 per cent of patients whose ulcers were injected, although a similar proportion of bleeding ulcers treated with 3 per cent sodium chloride (68 per cent), 50 per cent dextrose (78 per cent) or normal saline (78 per cent) also achieved permanent haemostasis. As already stated[48,55], the injection of alcohol into the gastric mucosa of dogs produces deep ulcers and such ulcers also commonly occur in the human oesophagus following injection sclerotherapy for varices. It is, therefore, not surprising that ulcer perforation has been noted following alcohol injection into a bleeding ulcer[45].

Table 3 Combination of adrenaline plus sclerosant *versus* adrenaline alone

				Rebleeding or uncontrolled haemorrhage			
Reference	Year	No randomized	Endoscopic finding	Combination	Adrenaline alone	*P*	Comment
Chung *et al*[52]	1993	200	Active bleeding	14 of 98	16 of 98	n.s.	Numbers refer to operations for further bleeding. Injection of 1:10000 adrenaline with or without sodium tetradecyl sulphate
Choudari and Palmer[51]	1994	107	Active bleeding (57) Non-bleeding visible vessel (50)	6 of 28 1 of 24	7 of 29 1 of 26	n.s. n.s.	1.100000 adrenaline and 5 per cent ethanolamine
Villanueva *et al*[71]	1993	63	Various stigmas	8 of 33	4 of 30	n.s.	1:100000 adrenaline with or without 1 per cent polidocanol

n.s., Not significant

Table 4 Controlled trials involving alcohol injection

				Rebleeding or uncontrolled bleeding			
Reference	Year	No. randomized	Endoscopic finding	Alcohol	Control	*P*	Comment
Pascu *et al.*[76]	1989	143	Various stigmas	2 of 65	10 of 78	<0·05	'Rebleeding' relates to need for surgical intervention. Reduced mortality rate in injected patients
Lazo *et al*[77]	1992	39	Non-bleeding visible vessel	2 of 25	8 of 14	<0·001	Reduced need for surgical intervention in treated patients
Chiozzini *et al.*[78]	1989	53	Active bleeding (6) Other stigmas (47)	2 of 16	5 of 19	n.s.	18 further patients randomized to 1:100000 adrenaline (two rebled)

n.s., Not significant

Table 5 Controlled trials involving injection with thrombin

Reference	Year	No randomized	Endoscopic finding	Uncontrolled haemorrhage or rebleeding: Thrombin	Uncontrolled haemorrhage or rebleeding: Other	*P*	Comment
Balanzo *et al.*[58]	1990	64	Various stigmas	6 of 32	5 of 32 (thrombin plus 1:10000 adrenaline)	n.s.	
Benedetti *et al.*[57]	1991	82	Active bleeding (20)	9 of 10	9 of 10 (polidocanol)	n.s	
			Non-bleeding visible vessel (62)	4 of 31	2 of 31 (polidocanol)	n.s.	
Moreto *et al.*[70]	1992	38	Various stigmas	1 of 19	8 of 19 (no injection)	<0.005	Thrombin injected with 5 per cent ethanolamine

n.s., Not significant

One small study[78] compared the efficacy of alcohol with dilute adrenaline injection therapy. It had insufficient power to detect differences in efficacy; a much larger study is needed. The evidence that alcohol stops active bleeding and prevents rebleeding is more convincing than that for the sclerosants ethanolamine, polidocanol and sodium tetradecyl sulphate. The potential for side-effects is probably higher for alcohol than for adrenaline and this may deter such a study.

Thrombin

Direct injection of thrombin into a bleeding ulcer (*Table 5*) may represent the most effective method of sealing the vessel. Groitl and Scheele[59] injected bovine thrombin into the ulcers of 11 patients and both stopped active bleeding and prevented rebleeding. They also suggested that the agent may have value in sealing anastomotic leaks.

Balanzo *et al.*[58] randomized patients who presented with active ulcer bleeding to 1:10000 adrenaline or to a combination of 1:10000 adrenaline and thrombin. Permanent haemostasis was achieved in a similar proportion in both groups. Benedetti and colleagues[57] randomized consecutive patients who presented with peptic ulcer bleeding to 1 per cent polidocanol or thrombin injection. Primary haemostasis was achieved in 90 per cent of those injected with polidocanol and in 87 per cent of thrombin-treated patients. Permanent haemostasis after repeated injection in patients with rebleeding was achieved in all but two cases.

Thrombin injection, therefore, does seem to be at least as effective as other modalities, although clinical trials to date have had insufficient power to determine whether it is any better (or worse) than other approaches. A trial that could answer such questions would need to be extremely large, because standard injection treatment is relatively effective and because at least some of the failures of each modality are due to inaccurate localization of the injected material rather than to differences in the capacity of the materials to thrombose vessels.

A particular risk of thrombin injection is that it might precipitate extensive intravascular thrombosis. In clinical practice this has not been observed, either in patients injected for peptic ulceration or in those treated for variceal bleeding. Bovine thrombin also carries the theoretical risk of inducing anaphylaxis and it may be unwise to inject the same patients repeatedly with this material.

When to inject and how often?

Endoscopic injection therapy undoubtedly improves prognosis. It seems reasonable to administer treatment as early as possible, despite the lack of evidence that very early therapy is better than injection performed on the next available routine endoscopy list[80]. Patients with active bleeding are best treated immediately after resuscitation but, for less urgent cases, the disadvantages of out-of-hours endoscopy performed with inexperienced assistance in suboptimal surroundings may outweigh the theoretical advantages of early treatment. Once endoscopic therapy has been carried out, the patient should be monitored carefully for evidence of further bleeding. Many endoscopists now advocate repeat endoscopy and further injection at intervals of 24 h until endoscopic stigmas have resolved[81].

Failures of endoscopic therapy

It may be argued that endoscopists can adversely affect outcome in patients who fail endoscopic therapy. Repeated endoscopy, a large blood transfusion and delayed surgical operation in those who ultimately fail attempted endoscopic haemostasis all increase the risk of death. Unfortunately accurate prediction cannot be made of who will fail to benefit from endoscopic treatment. Patients with the most active, profuse haemorrhage are the least likely to respond to the non-operative approach, both because massive bleeding can make administration of endoscopic therapy impossible and because large holes in major arteries are unlikely to respond to any endoscopic treatment. Patients who are shocked, with active bleeding from a posterior duodenal ulcer or a high lesser-curve gastric ulcer, tend to comprise the failures in clinical trials[82–84]. Nevertheless, even in such patients the author's group has reported a 75 per cent success rate using treatment by injection or heater probe[82].

One approach in patients at highest risk is early repeat endoscopy with further treatment, even in the absence of rebleeding. Villanueva *et al.*[81] suggested that such a policy might improve outcome. The policy in those who rebleed after endoscopic treatment is not clear. Many endoscopists tend to retreat such patients, while others believe that rebleeding is an indication for surgical intervention[85–87]. Clinical trials do not fully define when to operate; although an aggressive, early, surgical approach has been reported as the best policy for elderly patients presenting with major ulcer bleeding[88], there are no data to support this notion for those receiving endoscopic therapy.

No study has compared surgery with endoscopic therapy. Most trials of endoscopic therapy define need for a surgical operation as a treatment failure. An alternative view is that endoscopic control of bleeding facilitates safe, early, elective surgery. A successful outcome in an individual patient often depends on a combination of endoscopic and surgical approaches; good management is a team approach.

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Announcement

Association of Gastrointestinal Surgeons of Great Britain and Ireland

This new Association will be formed under the umbrella of the Association of Surgeons of Great Britain and Ireland (ASGBI) and at the request of many of the Fellows of that Association. It will embrace the science and practice of surgery of the oesophagus, stomach, duodenum, jejunoileum, liver, gallbladder, biliary tree, pancreas, portal vein and spleen. As general surgery in Britain ramifies into groupings such as vascular, breast, endocrine, transplant surgery and coloproctology, so each is developing its own professional organization. The new Association of Gastrointestinal Surgeons is created to represent those with either an oesophagogastric or an HPB (hepatopancreatobiliary) interest, since it is anticipated that these two disciplines will remain closely linked for the foreseeable future. The Association will provide a structure for education and training, clinical developments and research into some of the most challenging diseases that confront surgeons today. Support, both practical and conceptual, has been offered by the Royal Colleges of Surgeons and the ASGBI, as well as by the leading experts in the field.

A Steering Group was established in 1995 to help bring the Association of Gastrointestinal Surgeons into being, to prepare a draft constitution and to arrange an inaugural meeting for more detailed discussion of aims and activities. This meeting will take place during the Annual Meeting of the ASGBI in Glasgow on the morning of Thursday 23 May 1996, with the following title and programme. We urge all those with an interest in the specialty to attend.

Gastrointestinal Surgery: Junctional Zones
10.30–12.15 hrs, 23 May 1996, Glasgow, UK

1 Scientific Update	
Zenker's diverticulum and the cricopharyngeus	T. N. Walsh
Splenectomy in the operative treatment of gastric cancer	D. Johnston
Papillary stenosis	R. C. G. Russell
Re-resection for hepatic metastases	M. Rees
2 Birth of the Association: live or still?	
Rationale and draft constitution	Steering Group

W. H. Allum
J. Bancewicz
G. Glazer
A. Watson
R. C. N. Williamson

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Annales de Chirurgie

Digest

For this quarter's digest, Drs Pascal Frileux and Denis Castaing, from *Annales de Chirurgie*, choose the best from issues eight, nine and ten of 1995. A reciprocal digest written by our European Editor, Colin Johnson, appears in the French journal.

Digestive system

Issue number 8 of *Annales de Chirurgie* is dedicated to clinical and research studies from the surgical community of Quebec and Montreal.

The first paper[1] is on the management of intrahepatic and common bile duct lithiasis by extracorporeal lithotripsy. Endoscopic sphincterotomy or percutaneous extraction of intrahepatic and common bile duct stones (through a T tube tract or by transhepatic access) may fail. Dagenais *et al.*[1] report on 18 patients (mean(s.d.) age 68·4(4·6) years) treated by extracorporeal shockwave lithotripsy combined with endoscopic sphincterotomy and/or percutaneous extraction. Seventy-two per cent of patients had previously undergone cholecystectomy and 44 per cent exploration of the common duct. Patients were submitted to a mean(s.d.) of 1·56(0·17) sessions of lithotripsy (5546(701) shockwaves). Mean(s.d.) hospital stay was 19·5(3·3) days. After lithotripsy, endoscopic or percutaneous procedures were necessary to clear the biliary tract with 1·17(0·19) sessions per patient. Success (clearance of all the stones) was obtained in 78 per cent of patients. The five failures were treated by endobiliary prosthesis (four patients) and cholecystectomy and bile duct exploration (one). The authors', conclusions were that lithotripsy in association with the usual therapeutic modalities, i.e. a multidisciplinary approach, increases the clearance rate and helps to avoid surgery in the majority of patients.

Multiple small bowel resections for obstructive symptoms caused by Crohn's disease may lead to a short bowel and malabsorption. Experience of strictureplasty was reported from the University of Montreal[2]. Between August 1983 and March 1993 Montreuil *et al.*[2] performed 90 strictureplasties in 25 patients. There were 13 men and 12 women with a mean age of 37 years. Fourteen had previously had small bowel resection for Crohn's disease. The mean number of strictureplasties per patient was 4·3. Concomitant resection of the bowel with active disease was performed in 18 patients. There was no perioperative death, and two patients developed four postoperative complications: enterocutaneous fistula, haemorrhage, bacteraemia and wound sepsis. After operation 18 patients were completely relieved of symptoms, six were improved and only one became worse. After a 27-month follow-up period, the symptoms recurred in 13 patients: three had no treatment, seven had medical treatment and three required reoperation. The authors conclude that these results support the safety and use of strictureplasty for stenotic bowel lesions in patients with Crohn's disease.

Ferraro *et al.*[3] report their experience of the use of the yttrium–aluminium–garnet (YAG) laser to treat 110 patients with irresectable oesophageal carcinoma. Patients were inoperable because of metastases (42 per cent), advanced systemic disease (23 per cent), extensive local disease (18 per cent) or recurrent carcinoma (17 per cent). There were 92 men of mean age 68·4 years and 18 women of mean age 67·0 years; 47 per cent of the patients had received no previous treatment while 53 per cent had been treated previously with either radiotherapy, chemotherapy, surgery, stents or dilatation. The majority of lesions were adenocarcinomas (57 per cent) and squamous cell carcinomas (37 per cent); 66 per cent of tumours were located in the distal third of the oesophagus. Patients received a mean of 2·4 laser treatments with a mean of 4883 joules per treatment. The rate of major complications was 3 per cent and the mortality rate was 2 per cent. Median survival for the group was 4·5 months. No significant difference was found in the length of survival according to the histology of the tumour ($P = 0{\cdot}35$), the presence of metastases ($P = 0{\cdot}24$) and the association of other treatment modalities with the laser ($P = 0{\cdot}06$). Functional results were considered good to excellent in 82 per cent of cases. The conclusion of the authors was that the YAG laser does not influence overall survival of inoperable patients, but is effective and safe.

Urology

Lymph node status in patients with cancer of the prostate is important in terms of prognosis and treatment choice. Saad *et al.*[4] report the practical value of prostate-specific antigen (PSA) to predict lymphatic spread in prostatic cancer, in an attempt to limit the number of lymph node dissections carried out for staging. A total of 240 consecutive patients with prostatic cancer and negative bone scans were studied, in whom preoperative PSA level and lymph node status (determined by lymphadenectomy) were known. Results showed that the risk of node-positive disease was highly correlated with PSA level and poorly correlated with clinical stage and histological grade. However, there was no minimum PSA level below which nodes were consistently negative. With a PSA level of less than 10 ng/ml 8 per cent of lymphadenectomies revealed positive nodes (two patients had a PSA value of 3 ng/ml). When the PSA concentration was between 10 and 20 ng/ml, 17 per cent had positive nodes, compared with 21 per cent with a PSA level between 20 and 50 ng/ml, and 53 per cent when the level was over 50 ng/ml. The combination of a low grade with histological PSA level of less than 20 ng/ml consistently identified a subgroup of patients with negative nodes. The authors concluded that estimation of PSA level may be of use in predicting lymph node status but cannot, at present, be used to replace lymphadenectomy.

A second urological paper[5] reports on antireflux procedure in children. Twenty-eight boys and 112 girls, with an age range of 4 months to 15 years (mean 5·8 years), were treated with a Lich–Gregoire antireflux operation. Twenty-seven of the 220 reimplanted ureters were duplicated. At 6 months' follow-up, ten of the 140 children had persistent reflux and five had contralateral reflux; two patients had obstruction and one needed reintervention. At 1-year follow-up, only three children had persistent reflux and none had contralateral reflux. The authors concluded that the Lich–Gregoire antireflux procedure is simple, with minimal morbidity and an excellent success rate.

Experimental studies

Several experimental papers on the vascular toxicity of cyclosporin A appear in issue number 8 of the *Annales de Chirurgie*.

The first paper[6] sought to determine the effect of cyclosporin A on coronary artery reactivity. Six mongrel dogs weighing 20–30 kg were anaesthetized with sodium pentobarbital and ventilated. A median sternotomy was performed to expose the heart. Left anterior and circumflex coronary flows were measured with an electromagnetic flowmeter. Heart rate, mean arterial pressure, coronary sinus pressure and the change in pressure over time (dP/dt) were monitored during all experiments. Blood samples were withdrawn from the coronary sinus to measure cyclosporin A concentration. Injections of 5 and 10 mg cyclosporin A in the left anterior descending coronary artery were administered to all animals and the measure of circumflex coronary blood flow was used as a control during the experiments. There was a mean(s.d.) decrease in blood flow in the left anterior descending coronary artery of 24(9) per cent ($P = 0{\cdot}002$) and 18(1·1) per cent ($P = 0{\cdot}009$) after 5 and 10 mg cyclosporin A respectively, and a mean(s.d.) increase in coronary vascular resistance of 31(12) per cent ($P = 0{\cdot}005$) and 16(24) per cent ($P = 0{\cdot}1$). There were no significant changes in circumflex coronary artery blood flow or in dP/dt during the experiments. Mean(s.d.) cyclosporin blood levels were 453(226) and 1087(199) nmol/l after injection of 5 and 10 mg cyclosporin A. In conclusion, this study suggests that cyclosporin A can cause acute vasoconstriction of the arterial coronary vessels.

Dagenais *et al.*[7] studied the effects of cyclosporin A on endothelial and smooth muscle reactivity in endothelium-regenerated arteries. Cyclosporin A affects vascular reactivity but its effect on local vascular tone following endothelial regeneration is unknown. Three groups of eight rats were subjected to mechanical denudation of the aortic endothelium. A first group was treated for 8 weeks with cyclosporin A by mouth (20 mg/kg) and a second group with an equivalent volume of cyclosporin A vehicle, i.e. olive oil. A control group was submitted to a standard diet. After 8 weeks, aortic rings were suspended in organ chambers for assessment of endothelial and smooth muscle function. Mean(s.d.) maximal endothelium-dependent relaxation to acetylcholine was 52(3) per cent in the cyclosporin A group, 50(4) per cent in the group receiving olive oil and 48(5) per cent in controls (*P* not significant). Adenosine diphosphate induced a mean(s.d.) relaxation of 30(7) per cent in the cyclosporin A group, 18(2) per cent in the group receiving olive oil and 24(5) per cent in controls (*P* not significant). Histamine produced a mean(s.d.) relaxation of 38(6) per cent in the cyclosporin A group, 43(4) per cent in the olive oil group and 47(5) per cent in controls (*P* not significant). In aortic segments studied without endothelium, the mean(s.d.) contraction increase induced by serotonin was 259(43) per cent in the cyclosporin A group, 153(11) per cent in the olive oil group and 243(24) per cent in controls ($P < 0{\cdot}05$, olive oil group *versus* the two others). Maximal tension to cumulative doses of noradrenaline was increased in rings without endothelium treated with cyclosporin A. All these differences were abolished in rings studied with endothelium. Endothelium-independent relaxation to sodium nitroprusside was similar in all groups. The authors conclude that cyclosporin A does not specifically affect endothelium-dependent relaxation of the regenerated aortic endothelium and suggest that the increases in vascular tone mediated by increased smooth muscle sensitivity to noradrenaline and serotonin are prevented by the regenerated endothelium (prevention of cyclosporin A-induced vascular toxicity).

Despatis *et al.*[8] analysed the effect of cyclosporin A on the peripheral venous system. Cyclosporin A was injected into an isolated hind limb saphenous vein perfused at constant flow in 29 dogs. Reactivity of the vein was tested by infusion of noradrenaline before and after cyclosporin A administration. In a group of seven dogs, cyclosporin A at doses of 5, 10 and 20 mg was infused over 20 min and injections of 6, 12 and 24 mg noradrenaline were given before and during cyclosporin A administration. In another group, ipsilateral lumbar sympathectomy was performed before cyclosporin A injection. The infusion of cyclosporin A over periods of 10 and 20 min did not cause significant changes in venous perfusion pressure. The infusion of 30 mg cyclosporin A over 60 min caused an increase in mean(s.d.) venous perfusion pressure from 44(2) to 58(5) mmHg ($P < 0{\cdot}0001$). Surgical sympathectomy prevented the venoconstriction response to cyclosporin A. Injections of cyclosporin A after 3, 6 and 12 mg noradrenaline significantly increased venous perfusion pressure. The authors conclude that cyclosporin A causes constriction of the vein through stimulation of the sympathetic nervous system and potentiates the venoconstrictor effect of noradrenaline.

Latulippe *et al.*[9] designed an *in vitro* experiment to study the effects of pentoxifylline on endothelium-dependent and -independent vasorelaxation of the rat thoracic aorta. Three groups of ten rats were treated for 4 weeks with cyclosporin A (30 mg per kg per day), cyclosporin A and pentoxifylline (40 mg per kg per day) or cyclosporin A and pentoxifylline (80 mg per kg per day). At the end of the period, rings (4–5 mm) of aorta were harvested and suspended in organ chambers containing Krebs–Ringer solution for assessment of endothelial and smooth muscle reactivity. Endothelium-dependent relaxation to acetylcholine was significantly enhanced in animals treated with cyclosporin A and pentoxifylline (40 mg per kg per day) compared with that in those exposed to cyclosporin A alone ($P < 0{\cdot}05$). Response to histamine and adenosine diphosphate was not affected. However, the use of pentoxifylline at 80 mg per kg per day significantly reduced the endothelial response to the same drugs ($P < 0{\cdot}05$), suggesting a detrimental effect of pentoxifylline at this concentration. Endothelium-independent relaxation to sodium nitroprusside was similar in all groups. The results suggest that the clinical benefit reported with the use of pentoxifylline in patients chronically exposed to cyclosporin A may partly be due to an improvement in vascular endothelial function. However, the toxicity encountered at high doses should caution its use in a clinical setting.

Thoracic surgery

Issue number 9 of the journal is dedicated to thoracic and cardiovascular surgery.

A case report from van Ruyssevelt *et al.*[10] described the repair of a ventricular rupture after valve replacement. A 70-year-old patient, who had required a Carpentier pericardial prosthetic valve for mitral valve replacement, developed a type 2 intraoperative left ventricular rupture (mid-portion of the left ventricle) with cataclysmic bleeding. A successful repair with an intraventricular Dacron (Du Pont, Wilmington, Delaware, USA) patch was performed by suturing the patch on the prosthetic sewing ring and through the ventricular wall with pledget stitches. The postoperative course was satisfactory, without angina and with reduced dyspnoea. Preoperative and postoperative left ventricular function were similar. These ventricular injuries after mitral surgery are well known but are always difficult to manage, and often fatal. The authors conclude that this technique (including prosthetic valve removal and intraventricular repair) provides a good chance of success, and they comment upon prevention: preserving the posterior mitral leaflet, avoiding extensive decalcification or resection, and using low profiled prosthetic mitral valves.

Massard *et al.*[11] reviewed a series of repeat pulmonary resections for recurrence of lung cancer. Ninety-three patients who had had a previous lobectomy for bronchogenic cancer and ipsilateral cancer recurrence were studied. Forty-six patients were rejected for oncological reasons (30 stage IIIb, 16 stage IV). Forty-seven patients (51 per cent) were resectable, but 17 did not undergo surgery for associated medical problems (11 patients) or refusal (six). The 30 patients operated on (29 men) had a mean age of 61 (range 47–72) years. The previous cancer was stage I in 26 patients and stage II in four. The mean interval between the first resection and recurrence was 30 (range 6–97) months. Three patients underwent exploratory thoracotomy: two had mediastinal involvement and one had pleural metastases. Twenty-two underwent a completion pneumonectomy, and five had miscellaneous conservative resections. There were four operative deaths, due to intraoperative bleeding, postoperative bleeding, pulmonary embolism and pneumonia. Four patients had non-fatal surgical complications: two clottings (re-exploration), one empyema (lavage) and one bronchopleural fistula (thoracoplasty). Resected patients were staged as follows: 13 stage I, four stage II, ten stage III. The survival rate following resection including operative mortality was estimated as 52 and 44 per cent at 3 and 5 years respectively. The authors conclude that repeat surgery conveys an increased risk but may achieve valuable long-term results.

Palmar hyperhidrosis, although a benign disease, is annoying to many patients. At present the best treatment for this condition is upper thoracic sympathectomy via many different approaches. The videothoracoscopic approach has been recommended as a minimally invasive procedure. Lévy *et al.*[12] report their 1-year experience with transaxillary endoscopic sympathectomy in 99 patients with palmar hyperhidrosis. Standard videothoracoscopy with standard laparoscopic instruments was used to perform sympathectomy via a transaxillary approach. The mean operating time was 12 min and mean hospital stay 32 h. The results in terms of warm and dry hands were excellent. Only one case of transitory Horner's syndrome was noted. The authors are convinced that thoracoscopic sympathectomy is the procedure of choice for the treatment of palmar hyperhidrosis because it is a relatively simple and effective procedure. The advantages are short recovery time and hospital stay along with excellent functional and cosmetic results.

Acquired immune deficiency syndrome and emergency abdominal operation

Hammoud *et al.*[13] reviewed the records of 34 human immunodeficiency virus (HIV)-positive patients operated on for an acute abdomen in 1986–1994. Eleven patients had no symptoms of acquired immune deficiency syndrome (AIDS) (Centers for Disease Control (CDC) stage I–II) while 23 had clinical signs of the disease with CDC stage IV-B to IV-E. Twelve patients presented with acute appendicitis. It was interesting to note that fever and leucocytosis were absent in patients with stage IV disease with appendicitis ($n = 6$) while these signs were present in the six with stage II disease. Eight patients had acute cholecystitis, of whom five had stage IV disease and no gallstones, and one had a specific pathogen (cytomegalovirus (CMV)); the remaining patients with cholecystitis were HIV positive with stage II disease and all had gallstones. Eight patients, all with stage IV disease, had generalized peritonitis due to perforation of the duodenum ($n = 2$), small bowel ($n = 5$) or colon ($n = 1$). The small bowel perforations were due to CMV infection ($n = 2$), *Mycobacterium avium intracellulare* ($n = 1$) or lymphoma ($n = 2$). The diagnosis of peritonitis was difficult and often delayed. The six remaining patients were suffering from Kaposi sarcoma ($n = 1$), colonic cancer ($n = 1$), trauma ($n = 1$), small bowel volvulus ($n = 2$), and rectal bleeding ($n = 1$).

Postoperative mortality was zero in the appendicitis group, two of eight in the cholecystitis group and four of eight in the peritonitis group, giving an overall mortality rate of 18 per cent (six of 34) and a mortality rate in patients with stage IV disease of 26 per cent (six of 23). Two additional stage IV patients recovered after the operation but died within 2 months from intercurrent disease. This series shows that asymptomatic HIV-positive patients have similar forms of acute abdomen as the rest of the population, while those with AIDS stage IV have specific intra-abdominal diseases and present with blurred symptoms, leading to delay in operation.

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SURGERY TODAY
The Japanese Journal of Surgery

Digest

This month's selection from the October to December 1995 issues of *Surgery Today* (*The Japanese Journal of Surgery*) is written by Professor K. Sugimachi. A digest of the *BJS* for the same period, written by Mr Colin Johnson, appears in the Japanese journal.

Stomach

The deleted-in-colorectal-cancer (*DCC*) gene, located on chromosome 18q21.3, is considered to be a tumour suppressor gene related to cellular adhesion receptors. Loss of heterozygosity on chromosome 18q is frequently observed in patients with adenomatous polyposis coli, as well as in those with sporadic colonic carcinoma and its liver metastases. This study[1] investigated the expression of *DCC* messenger RNA (mRNA) in the resected specimens of 38 patients with gastric cancer and 28 with colorectal cancer by a reverse transcription–polymerase chain reaction method. In patients with gastric cancer the mean level of expression of *DCC* mRNA in the tumours was significantly lower than that in normal tissues, but no difference was observed in patients with colorectal cancer. *DCC* mRNA expression was decreased in 15 of the 38 patients with gastric cancer and in ten of the 28 with colorectal cancer, and there was a significant correlation between decreased expression of *DCC* mRNA and nodal metastasis in patients with colorectal cancer. Two of four patients with gastric cancer and none of seven with colorectal cancer whose cancers were confined to the muscularis propria without metastasis showed decreased expression of *DCC* mRNA. These findings demonstrate that decreased expression of *DCC* mRNA may occur at an early stage in gastric cancer and at a late stage in colorectal cancer, and that this decreased expression correlates with the potential to develop nodal metastasis.

Sixty-two overweight patients with gastric cancer were compared with 201 of normal weight to clarify the influence of excessive weight on the surgical treatment of gastric cancer[2]. The frequency of hypertension and diabetes mellitus was significantly higher in the overweight patients, but no pathological differences in the resected tumour were found between the two groups. Operating time was longer and the number of lymph nodes extirpated and examined was smaller in the overweight group. The incidence of postoperative complications was not higher in overweight patients. The postoperative survival rate of patients with nodal metastasis was statistically lower in the overweight group. Regarding the cause of death in patients with nodal metastasis, 61 per cent of overweight patients and 44 per cent of those with normal weight died from recurrence of gastric cancer. In conclusion, surgical treatment of overweight patients with gastric cancer was found to be technically more difficult and the prognosis of such patients with nodal metastasis may thus be worse than that of their normal-weight counterparts.

The possible factors contributing to a delayed return of gastric emptying after gastrojejunostomy were analysed by means of a review of 955 consecutive patients who had undergone gastric surgery for the first time, which revealed 23 who had experienced delayed gastric emptying[3]. Of seven consecutive patients who had undergone reoperation for postsurgical gastroparesis syndrome, three were found to have experienced persistent delayed emptying. Significant factors were age over 60 years and a history of non-resectional gastric bypass, Roux-en-Y reconstruction or reoperation for pre-existing postoperative gastroparesis. There was a higher incidence of delayed emptying in those who had had a vagotomy, and nutritional indices increased as patients recovered from delayed emptying; however, vagotomy and malnutrition could not be considered independent variables. In the event of delayed gastric emptying, a long period of supportive treatment is required to avoid an unnecessary second operation as most patients recover spontaneously, whereas a high incidence of persistent delayed emptying may occur after early reoperation.

Colon

Using a new transcutaneous magnetic stimulation technique, sacral nerve terminal motor latency (SNTML) was measured after ileal J pouch–anal anastomosis in eight patients with ulcerative colitis, and the results were compared with those obtained from 15 normal subjects[4]. The conduction delay of SNTML in patients with soiling was significantly longer than that of the continent group as well as that of normal subjects. There were no significant differences in conduction delay between the continent group and control subjects. These findings support the hypothesis that such soiling, which is sometimes seen after ileal J pouch–anal anastomosis, is partly due to damage to the sacral nerves.

To determine the influence of anal canal sensation on anal function after low anterior resection (LAR) for rectal cancer, anal canal sensation was quantitatively evaluated before and after LAR by measuring anal mucosal electrosensitivity (AMES), and the relationship between AMES and postoperative anal function was explored[5]. Sensory thresholds 1, 2 and 3 cm from the anal margin were recorded in 21 patients who underwent LAR for rectal cancer (LAR-I) before, then 1 and 4 months after, operation. A further 14 patients who had been followed for more than 1 year after LAR (LAR-II) and 21 control subjects were also studied. The median preoperative sensory threshold in the LAR-I group was higher than that in controls, although the difference was not significant. The sensory threshold in the LAR-I group 4 months after LAR was lower than that obtained before operation, but did not differ significantly from that in the LAR-II and control groups. Although the postoperative sensory threshold did not correlate with postoperative anal function, the preoperative threshold was higher in patients who were experiencing episodes of faecal incontinence 4 months after operation. These results suggest that preoperative measurement of AMES is useful for identifying patients who are likely to have a poor quality of continence after LAR.

The value of venous invasion as a prognostic factor was evaluated in 124 patients with colorectal cancer[6]. By classifying the patients as having either negative or mild invasion, or moderate to marked invasion, a significant correlation was found between the degree of venous invasion and clinicopathological variables such as lymphatic invasion, lymph node metastasis, liver metastasis and DNA ploidy. Those with a lower degree of vascular invasion demonstrated significantly more favourable survival; however, of the six prognostic factors analysed by the Cox proportional hazard model, the only significant factors were depth of invasion and DNA ploidy. Although venous invasion was of no significance, it is still considered a valuable prognostic indicator that is easy and economical to perform.

Liver

The role of glucagon as a mediator of gastric hyperdynamic circulation, induced by carbon tetrachloride, was assessed in cirrhotic rats[7]. Selective elimination of pancreatic glucagon from the circulation was achieved by intravenous infusion of a glucagon antiserum. Gastric blood flow was measured by laser Doppler flowmetry. Glucagon antiserum had no effect on blood flow in the stomach of control rats, while in rats with cirrhotic portal hypertension, glucagon antiserum reduced gastric blood flow significantly (by 30 per cent). Glucagon antiserum did not completely exclude the gastric hyperdynamic state in the cirrhotic rats. It would thus appear that glucagon contributes to the gastric hyperdynamic circulation associated with cirrhotic portal hypertension.

Prostaglandin (PG) E_2 is generally accepted to be an immunosuppressant produced by cancer cells and their surrounding macrophages. Although several investigators have reported the detection of high concentrations of PGE_2 in the portal vein of patients with colorectal cancer, the relationship between these high concentrations and liver-associated immunity remains unclear. Another study[8] has attempted to determine whether portal administration of PGE_2 suppresses the immune function of the liver in a rat model. Donryu rats were given PGE_2 via the portal vein for 7 days, after which the cytotoxic activity of hepatic sinusoidal lymphocytes (HSLs) against natural killer (NK)-sensitive YAC-1 and rat syngeneic AH60C tumour cells was assessed. Purified HSLs are spontaneously cytolytic; however, the continuous administration of PGE_2 dramatically suppressed their cytotoxic activity in a dose-dependent fashion. Flow cytometric analysis showed that the large granular lymphocyte fraction, hepatic NK (pit) cells, and $CD4^-8^+$ killer–suppressor T cells were mainly reduced in number in the HSLs following PGE_2 infusion. In this rat AH60C metastasis model, the continuous administration of PGE_2 increased the number and size of metastatic tumour nodules in the liver, suggesting that high concentrations of PGE_2 in the portal vein suppress liver-associated immunity and promote the development of hepatic metastasis.

Vascular

A midterm follow-up of 150 claudicants was carried out after vascular reconstruction, by assessing cumulative patency, survival and palliation (graft patency in live patients) rates[9]. Eighty-nine claudicants (group I) underwent direct (*in situ*) proximal revascularization, 33 (group II) had indirect (*ex situ*) proximal revascularization, while 28 (group III) had distal revascularization. The secondary patency rate at 3 years was 97 per cent in group I, 97 per cent in group II and 75 per cent in group III. Only one patient with limb thrombosis required below-knee amputation. There were three perioperative deaths (two in group I and one in group II). The survival rate at 3 years was 86 per cent in group I, 69 per cent in group II and 98 per cent in group III. The palliation rate at 3 years was 85 per cent in group I, 70 per cent in group II and 78 per cent in group III. These findings indicate the midterm benefits of suprainguinal and infrainguinal arterial reconstruction, and also suggest that important variables in the treatment of claudicants include the preoperative assessment of risk in individual patients, selection of the appropriate operative procedure and graft material, and intensive postoperative follow-up, as well as management of any associated disease.

The influence of the atherogenic response on restenosis after transluminal balloon angioplasty and the anastomosis of arterial reconstruction was investigated[10]. Iliac transluminal balloon angioplasty was performed on 81 consecutive patients at 86 sites, between January 1987 and December 1992. Balloon angioplasty alone was performed in 58 patients at 60 sites, while distal revascularization was performed in 23 patients on 26 limbs, in association with the angioplasty. An improvement in the inflow of the distal grafts was achieved in 22 of the 26 limbs. The combined distal revascularization included 21 femoropopliteal bypasses, three femorofemoral bypasses and two thromboendarterectomies at the profunda femoris arteries. A reduction in luminal diameter after balloon angioplasty was determined by means of follow-up arteriography, which showed no obvious progression of the restenosis at the angioplasty sites even when neointimal hyperplasia had developed at the anastomosis of the arterial reconstruction. The cumulative graft patency rate of the combined distal revascularization did not differ significantly from that of femoropopliteal reconstructions alone during the study period. This study demonstrated that concomitant surgical insults do not have a detrimental effect on restenosis at angioplasty sites.

A retrospective analysis of the long-term behaviour of 111 glutaraldehyde-tanned human umbilical vein (HUV) grafts implanted between September 1977 and December 1993 was conducted[11]. A total of 81 patients, with a mean age of 68·7 years, received the grafts and were followed for 1–131 months. The 5-year primary cumulative patency rate for above-knee femoropopliteal bypass was 83 per cent, whereas that for other bypasses was 61 per cent. Aneurysm of the graft was defined as a physically apparent localized dilatation; diffuse ectasia was excluded. There were 11 aneurysms in nine grafts, two of which arose at the factory-made suture lines. The cumulative incidence of aneurysm had reached 22 per cent at 6 years. One aneurysm compressed the graft and resulted in limb-threatening ischaemia and another resulted in frank rupture. Moreover, reinforcement of the mesh did not prevent aneurysm development, the repair of which is mandatory because of the risk of rupture and acute thrombosis. HUV grafts showed an acceptable patency rate in the above-knee location, but the incidence of aneurysm formation after 5 years was abnormally high. Thus, both the risks and benefits of HUV grafts must be taken into account when considering their clinical application.

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Der Chirurg

Digest

For this quarter's digest Professor Christian Herfarth and Dr Thomas Lehnert have selected the best from the October to December 1995 issues of *Der Chirurg*. A digest of the *BJS* for the same period, written by Mr Colin Johnson, appears in the German journal.

Endotracheal tube fire

> *'It is essential that we learn from our own mistakes, but it is better if we can learn from the mistakes of others'*
> (Kirk-Stoddard. *Compliations of Surgery of the Upper Gastrointestinal Tract.* Baillière Tindall, 1986).

Tracheostomy for patients requiring long-term respiratory support is a routine procedure. Several instances of endotracheal tube ignition associated with the use of electrocautery or laser therapy have been reported in the literature, but still this complication occurs. Comberg *et al.*[1] report another instance of this potentially preventable complication. They recommend avoiding the use of monopolar electrocautery. If for some reason this is deemed indispensible, oxygen concentrations as low as possible should be used for ventilation and nitrous oxide should be avoided completely. Filling the cuff with saline rather than air and provision of gauze pads moistened with saline to extinguish possible fires quickly are additional precautions. The use of special non-inflammable endotracheal tubes is also possible, but costly. If a tube fire does occur, the burning tube must be removed immediately and the trachea should be cooled with cold saline to minimize thermal injury. A new tube is then inserted and the injury to the trachea and bronchial system is inspected endoscopically. Since tube fires may cause development of toxic gases the use of corticosteroid aerosols is recommended to prevent pulmonary oedema.

Surgical oncology

While treatment of gastrointestinal primary tumours is part of the daily workload of general surgeons, the treatment of tumour recurrence is often performed in centres with a special interest in surgical oncology. Pelvic recurrence of rectal carcinoma is particularly challenging since it may be disabling to the patient and extensive surgical procedures may be needed to cure, or at least relieve, symptoms. Schumpelick and Braun[2] from Aachen report their experience with 101 patients presenting with local recurrence of rectal carcinoma treated between 1980 and 1994. In this retrospective study 72 per cent of patients were symptomatic at the time of diagnosis of recurrence. Primary tumours were in Dukes stage A ($n = 18$), stage B ($n = 20$), stage C ($n = 50$) and stage 'D' ($n = 8$). Primary tumour stage was unknown in five patients. Three-quarters (71 per cent) of the recurrences were diagnosed within 2 years of resection of the primary carcinoma. Fourteen patients had intraluminal recurrence, 59 had extraluminal pelvic recurrence and 28 had additional distant metastases. Radical resection of recurrent tumour (R$_0$ resection) was possible in 51 patients, while 26 had microscopic or macroscopic tumour residues. Local tumour reduction was accomplished in 13 patients with irresectable distant metastases. No tumour reduction was possible in 11 patients. Multivisceral resection was performed in 48 patients.

The 5-year survival rate for the whole group of 101 patients was 10 per cent. The rate was only marginally better in 77 resected patients at 13·5 per cent, but in 16 treated with complete tumour resection (R0) and intraoperative radiotherapy it was 27 per cent and local tumour control was achieved in 50 per cent. The authors conclude that radical resection of pelvic tumour recurrence can be performed with acceptable mortality and morbidity rates and that this procedure offers excellent local tumour control and survival in patients with complete resection and negative margins.

The value of intraoperative radiotherapy was investigated in another study from Heidelburg[3] where this procedure has been used in the treatment of retroperitoneal sarcoma. This tumour has a high local recurrence rate and surgical resection is difficult owing to the close proximity of vital structures and the lack of fascial planes. Between June 1988 and December 1993 a total of 31 operations for primary and recurrent retroperitoneal sarcoma was performed in 25 patients. Eleven patients received intraoperative radiotherapy (10–24 Gy) plus postoperative external-beam radiotherapy (34–46 Gy); 14 were treated by postoperative external-beam radiotherapy (50 Gy) without intraoperative radiotherapy. Both groups were comparable with regard to tumour grading, although slightly more patients in the intraoperative radiotherapy group were in stage IVb. In both groups 55 per cent of operations were considered radical with no evidence of microscopic or macroscopic tumour residues. Perioperative complications were recorded in three of 11 operations with and in five of 20 without intraoperative radiotherapy. No surgical complications were observed following intraoperative radiotherapy. One patient died from underlying heart disease in the no intraoperative radiotherapy group. Local control at 2 years was 70 per cent in patients receiving intraoperative radiotherapy *versus* 30 per cent in those without, and the overall survival rate was 77 *versus* 39 per cent at 2 years. Although this was not a randomized study, the results indicate that intraoperative radiotherapy can be administered without increased postoperative morbidity, while local tumour control and overall survival rates appear to be improved.

The general principles for operative treatment of soft tissue sarcoma and special aspects of sarcoma in specific locations, such as the trunk and abdominal wall, are reviewed by Karakousis in two contributions[4,5]. Using adequate surgical techniques for incision and reconstruction, tumour resection rates of 95 per cent can be achieved in soft tissue sarcomas of the chest and abdominal wall. When a mesh is used for reconstruction of the abdominal wall, care should be taken to avoid direct contact between the mesh and loops of bowel. Interposition of tissue such as omentum or a rectus muscle flap significantly reduces the incidence of fistula. When the inguinal ligament has to be resected for sarcoma of the groin or upper thigh, mesh repair should avoid contact between the mesh and the femoral vessels. In this case a sartorius muscle flap may be interposed.

Inguinal hernia

Laparoscopic inguinal hernia repair was compared with open herniorrhaphy in a randomized trial by Leibl and associates[6] from Stuttgart. Between May and December 1993, 102 patients with direct or indirect unilateral inguinal hernia were randomized to either laparoscopic surgery ($n=54$) or open Shouldice repair ($n=48$). For laparoscopic hernia treatment the transperitoneal route with a 10 × 12-cm polypropylene mesh repair was used. The mesh was implanted subperitoneally and patients undergoing laparoscopy received a single dose of antibiotic prophylaxis. The groups were comparable with regard to sex, age, length of hernia history, occupational physical activity and previous abdominal operations. Patients with scrotal hernia, previous lower median laparotomy or with American Society of Anesthesiologists scores greater than 2 were excluded. Endpoints of the study were postoperative complications, analgesic medication, mobilization, time off work and hernia recurrence. Median operating times were 48 min for Shouldice repair and 65 min for the laparoscopic procedure. The laparoscopic hernia repair could be performed in all patients. Two patients required reoperation following Shouldice repair to relieve postoperative scrotal swelling. One additional patient in the Shouldice group required operative evacuation of postoperative haematoma. Two patients in the laparoscopy group required laparoscopic haematoma evacuation. Wound or graft infection was not observed in either group.

Postoperative spontaneous mobility was better in patients having the laparoscopic procedure. These patients also required less postoperative analgesia. On the second postoperative day 56 per cent of patients in the Shouldice group, but only 7 per cent in the laparoscopy group, required analgesic medication ($P<0{\cdot}001$). Median time off work was 38 days for patients undergoing Shouldice repair compared with 21 days after the laparoscopic procedure.

Patients were followed regularly at 1, 6 and 12 months by clinical examination and inguinal ultrasonography. No patient developed signs or symptoms of recurrent hernia, but patients tended to complain of postoperative discomfort more frequently after the open operation. At 1 year, 22 of 48 patients having the open procedure had complaints, compared with only eight of 53 treated laparoscopically ($P<0{\cdot}001$). The authors comment critically, however, that the rating of patient comfort may have been influenced by the patient's knowledge of the type of operation performed. They conclude that laparoscopic hernia repair provides better patient comfort and affords earlier return to work, although immediate costs are higher.

Spontaneous pneumothorax

Minimally invasive techniques have long been employed for thoracic surgical procedures. The group from Giessen reports on the use of thoracoscopy for primary and secondary spontaneous pneumothorax[7,8]. Between January 1990 and April 1994 a total of 49 operations was performed in patients with spontaneous pneumothorax. Primary pneumothorax had developed in 35 patients and secondary pneumothorax was diagnosed in 14. In patients with primary pneumothorax thoracoscopic treatment was indicated because of recurrent or persistent pneumothorax or haemothorax following primary drainage. In eight patients with primary pneumothorax thoracoscopy was performed as first-line treatment. Bullae were treated by ligation and/or stapler resection in 26 patients. Pleurodesis was performed in 20 patients, and 12 had resection of the parietal pleura. Major complications were not recorded, but in two patients the thoracoscopic operation had to be converted to open surgery. Mean postoperative hospital stay was 9 (range 5–16) days.

At a median follow-up of 19 (minimum 7) months, four patients had recurrent pneumothorax. Both patients with complete recurrence required thoracotomy, while no further treatment was deemed necessary in the two with partial recurrence. At follow-up ten of 33 patients treated thoracoscopically had sensory neurological deficits due to intercostal nerve injury and two of these ten also had sympathetic nerve injury. Five patients complained of severe pain syndromes and a further five had minimal non-specific complaints. Intercostal nerve injury was more frequent following pleural resection (seven of 12 patients) than after coagulation of the pleura (six of 17).

In ten of 14 patients with secondary pneumothorax the operation could be completed thoracoscopically, while four required conversion to thoracotomy. Thoracotomy was indicated because of extensive adhesions, persistent bronchopleural fistula following lobar resection or technical problems. No major intraoperative complications were recorded. A further three patients had prolonged postoperative fistula for 30–43 days. Two of these patients were physically unfit for thoracotomy. The authors conclude that thoracoscopic treatment of secondary pneumothorax, although not always successful, is indicated as first-line treatment in this group of severely ill patients. Conversion to open thoracotomy did not result in adverse events.

Desmoid tumours in familial polyposis

Colorectal cancer in patients with familial polyposis can now be effectively prevented by prophylactic proctocolectomy with ileoanal pouch reconstruction. The wider use of this operation has resulted in a shift of the causes of death in these patients. Most succumb to periampullary carcinoma or desmoid tumours. Since the institution of the Heidelberg familial polyposis registry in 1991, the incidence of desmoid tumours has been recorded prospectively in 171 patients[9]. A total of 29 patients with desmoid tumours was identified (17 per cent). Complete resection of the desmoid tumour (R_0) with wide margins was accomplished in 12 patients. Three of these patients developed recurrence, eight are recurrence-free and one refuses further evaluation. Tumour debulking was performed in six patients and was followed by aggressive progression of the desmoid despite additional treatment with tamoxifen and sulindac. Medical treatment with these drugs was beneficial in five of seven patients. In four patients tumour growth was arrested and in one the abdominal wall tumour was reduced in size. In life-threatening situations chemotherapy and radiotherapy may be considered. Radiotherapy resulted in tumour reduction in two women. Operative trauma from previous colectomy is considered the most important factor related to growth of intra-abdominal desmoid tumours in patients with familial polyposis. Eleven of 22 tumours were diagnosed within 2 years of the operation and 18 of 22 became apparent within 4 years after colectomy. The precise treatment modalities for desmoid tumours have yet to be established, since surgical treatment is followed by a high recurrence rate even if the tumours have been removed with an apparently wide margin. Palliative resections leaving macroscopic tumour residues behind are often followed by aggressive progression of the desmoid tumour. For large desmoids in which complete surgical removal is unlikely, conservative treatment with tamoxifen and sulindac is advocated.

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Radical surgery for advanced gallbladder carcinoma

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Forty-four patients with advanced gallbladder carcinoma (18 with stage pT_3 and 26 with stage pT_4 of the Union Internacional Contra la Cancrum classification) were aggressively managed by extended heptatic resection in 33 patients, bile duct resection in 28, pancreaticoduodenectomy in seven, gastrointestinal resection in eleven and portal vein resection and reconstruction in seven. Adjacent organ involvement was classified as follows: type I, hepatic involvement with or without gastrointestinal invasion (Ia, Ib); type II, bile duct involvement with or without gastrointestinal invasion (IIa, IIb); type III, hepatic and bile duct involvement with or without gastrointestinal invasion (IIIa, IIIb); type IV, gastrointestinal involvement without hepatic or bile duct invasion. Fourteen of 15 patients with type I tumours had a curative resection compared with seven of 26 with type III lesions ($P < 0{\cdot}0001$). The surgical mortality rate was two of 15 patients with type I tumours, seven of 26 with type III tumours and nine of 44 for the whole group. The long-term survival rate after curative resection was four and two of 23 at 3 and 5 years respectively, significantly better than two and none of 21 at 1 and 2 years after non-curative resection ($P < 0{\cdot}01$). The survival rate after curative resection for patients with type I tumours was four and two of 14 at 3 and 5 years respectively, significantly better than for other types ($P < 0{\cdot}05$). This classification of advanced gallbladder carcinoma according to involvement of adjacent organs might be helpful in planning surgery for this condition; in particular, type I tumours should be treated by a radical surgical procedure to achieve a favourable outcome.

Surgical treatment of gallbladder carcinoma has not achieved favourable results[1–3]; 5-year survival rates range from 5 to 40 per cent[1–4]. Prognosis is closely correlated with the extent of invasion, suggesting that survival is stage dependent[4–6]. Patients with early gallbladder carcinoma have long-term survival rates higher than 70 per cent at 5 years[3–6]. Advanced gallbladder carcinoma with invasion into adjacent organs such as the liver, bile

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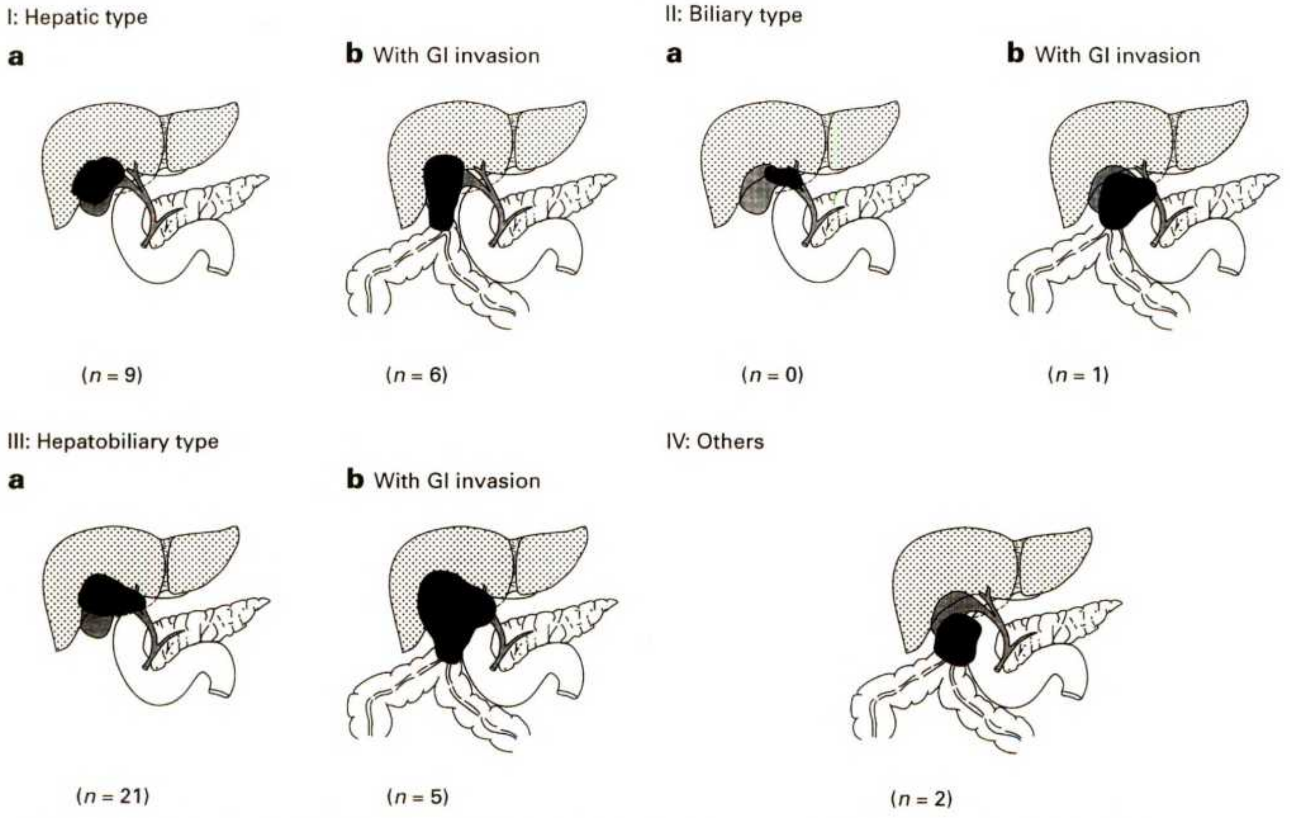

Fig. 1 Classification of advanced gallbladder carcinoma according to involvement of adjacent organs. GI, gastrointestinal

duct, duodenum and colon is in most cases irresectable, or results in a poor outcome even if resection is possible[1,5,7]. Recent reports have suggested that, while aggressive surgery for advanced gallbladder carcinoma has improved prognosis[8,9], morbidity and mortality rates are increased, especially when extended hepatic resection is necessary. Advanced biliary tract carcinoma is often accompanied by obstructive jaundice, suggesting an association with increased surgical morbidity and mortality rates[9,10].

In this study the effect of an extended surgical approach on the prognosis of advanced gallbladder carcinoma was evaluated retrospectively.

Patients and methods

All patients with advanced gallbladder carcinoma admitted to the First Department of Surgery of Chiba University Hospital between November 1980 and January 1994 were included in this study. Cancers were classified by stage using the criteria of the Union Internacional Contra la Cancrum[11]. Advanced gallbladder carcinoma consisted of cases of stage pT_3 and pT_4. Medical records were reviewed retrospectively. Forty-four patients aged 44–78 (mean 63·4) years (15 men and 29 women) had a surgical resection. Tumour staging was as follows: 18 patients had pT_3, 26 had pT_4 and 13 had pN_0, nine had pN_{1a} and 22 had pN_{1b}. No patient had distant metastasis to any organ except the liver.

Adjacent organ involvement was classified as follows: type I, hepatic involvement with or without gastrointestinal invasion (Ia, Ib); type II, bile duct involvement with or without gastrointestinal invasion (IIa, IIb); type III, hepatic and bile duct involvement with or without gastrointestinal invasion (IIIa, IIIb); type IV, gastrointestinal involvement and others (*Fig. 1*). The 44 patients were grouped as follows: 15 patients had type I involvement (nine with Ia, six with Ib); one had type II (IIb); 26 had type III (21 with IIIa, five with IIIb), and two had type IV (one with IVa, one with IVb). The surgical procedures performed are listed in *Table 1*. Seven patients who had gallbladder bed resection were excluded from the hepatectomy group (33 patients) and defined within the no hepatectomy group (11)[12].

Thirty-nine patients had adenocarcinoma, while there were three adenosquamous and two undifferentiated carcinomas. All patients had direct extension to the adjacent organs. 'Curative' resection in which the surgical margin was histologically free from cancer invasion was performed in 23 patients and non-curative resection in 21. Mean follow-up was 69 (range 3–174) months, and was complete. Survival curves were constructed using Kaplan–Meier analysis[13]. Statistical assessment of survival was performed with a generalized Wilcoxon test. Comparison between type I and III involvement was made by Fisher's exact test.

Table 1 Operative procedures for advanced gallbladder carcinoma

Operative procedure/Combined resection	No. of patients*
No hepatectomy group	11
Cholecystectomy	
Cholecystectomy alone	4
Gallbladder bed resection	1
Gallbladder bed resection plus bile duct resection	3 (1)
Gallbladder bed resection plus pancreaticoduodenectomy	2
Gallbladder bed resection plus bile duct resection plus duodenal wedge resection	1
Hepatectomy group	33
Central inferior hepatectomy (S4a plus S5)	11
Hepatectomy alone	2
Bile duct resection	4 (1)
Pancreaticoduodenectomy	1
Colonic resection	1
Bile duct resection plus duodenal wedge resection	1
Pancreaticoduodenectomy plus colonic resection	2
Extended right hepatectomy	18
Hepatectomy alone	1
Bile duct resection	13 (4)†
Bile duct resection plus colonic resection	2
Bile duct resection plus gastrectomy plus colonic resection	1
Pancreaticoduodenectomy plus colonic resection	1
Extended left hepatectomy	1
Bile duct resection	1
Right trisegmentectomy	3
Bile duct resection	1 (1)†
Bile duct resection plus colonic resection	1
Pancreaticoduodenectomy plus colonic resection	1

*Values in parentheses are the number of patients undergoing portal vein resection and reconstruction. †Includes one patient with inferior vena cava resection and reconstruction

Results

A comparison of patient characteristics and operative procedures was made (*Table 2*). There were no differences in age, sex or tumour staging. Portal vein resection was carried out more frequently for type III than for type I tumours (six of 26 *versus* none of 15 respectively, $P<0.05$). Twenty-three of the 44 patients had curative resection (*Table 3*). Fourteen of 15 patients with type I involvement had a curative resection compared with seven of 26 with type III disease ($P<0.0001$). No difference was

Table 2 Patient characteristics

	Type of gallbladder carcinoma				
	I	II	III	IV	Total
Sex ratio (M : F)	7 : 8	0 : 1	8 18	0 · 2	15 : 29
Mean(s.e.m.) age (years)	65·2(9·8)	69	61·7(9·5)	65·5(0·7)	63·4(9·4)
$pT_3 : pT_4$	8 : 7	0 : 1	8 : 18	2 : 0	18 : 26
$pN_0 . pN_{1a} : pN_{1b}$	7 : 4 : 4	0 : 1 : 0	6 . 4 : 16	0 . 0 : 2	13 : 9 . 22
Type of operation					
Hepatic resection	12	1	19	1	33
Bile duct resection	10	0	18	0	28
Gastrointestinal resection	5	1	5	0	11
Pancreaticoduodenectomy	1	1	4	1	7
Portal vein resection*	0	1	6	0	7
Inferior vena cava resection	0	0	2	0	2

*$P < 0.05$ (group I *versus* group III, Fisher's exact test)

Table 3 Operative curability according to the extent of adjacent organ involvement

	Resection		
Type	Curative	Non-curative	Total
I	14*	1*	15
a	9	0	9
b	5	1	6
II	1	0	1
a	0	0	0
b	1	0	1
III	7*	19*	26
a	6	15	21
b	1	4	5
IV	1	1	2
Total	23	21	44

*$P < 0.0001$ (type III *versus* type I, Fisher's exact test)

Table 4 Surgical morbidity and mortality according to type of advanced gallbladder carcinoma

	Morbidity			
Type	Minor	Major	Total	Mortality
I	2	3	5 of 15	2 of 15
II	0	1	1 of 1	0 of 1
III	4	10	14 of 26	7 of 26
IV	0	0	0 of 2	0 of 2
Total	6	14	20 of 44	9 of 44

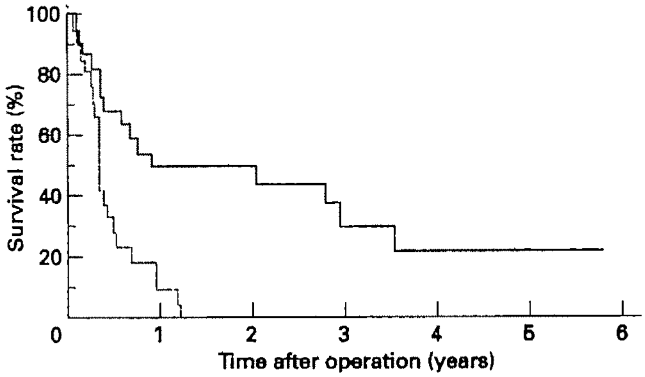

Fig. 2 Survival following curative (——; $n = 23$) and non-curative (-----; $n = 21$) resection. $P < 0.01$ (curative *versus* non-curative resection, generalized Wilcoxon test)

demonstrated between type a and b involvement in each group.

The overall surgical morbidity rate was 20 of 44 patients and mortality rate was nine of 44 (*Table 4*). Patients with type III tumours had a surgical morbidity rate of 14 of 26 and mortality rate of seven of 26, higher than five of 15 and two of 15 respectively in patients with type I tumours. Postoperative complications included hyperbilirubinaemia (12 patients), disseminated intravascular coagulation (four) rupture of a pseudoaneurysm (one), pleural effusion (four), pneumonia (three) and biliary fistula (five). The most frequent cause of death was hepatic failure (seven of nine deaths). Mean survival was 730 days for patients following curative resection and 124 days after non-curative resection. Late survival was significantly worse in the latter group (*Fig. 2*). Survival was significantly better for patients with type I tumours compared with the rest (*Fig. 3*); seven of 14 patients with type I tumours are still alive. Twelve patients developed recurrence after curative resection, which was local in six, involved hepatic metastasis in three, pulmonary metastasis in two, cerebral metastasis in one and was generalized in one.

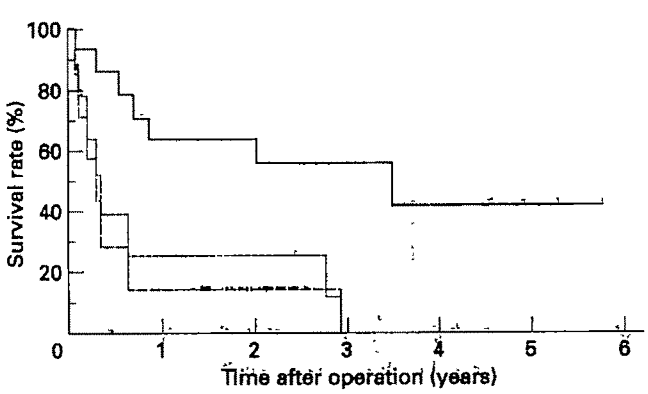

Fig. 3 Survival after curative resection in 30 patients according to involvement of adjacent organs (see *Fig. 1* for classification). ——, Patients with type I tumours ($n = 14$); -·-·-, patients with type II, III and IV tumours ($n = 9$); ——, patients with type III tumours ($n = 7$). $P < 0.05$ (type I *versus* type III and types II, III and IV, generalized Wilcoxon test)

Discussion

Recent advances in diagnostic methods such as ultrasonography and computed tomography have increased the early detection of gallbladder carcinoma[14,15]. However, most patients have advanced disease at diagnosis because early tumours are not symptomatic except in cases with concomitant gallstones[5].

Advanced gallbladder carcinoma usually extends into adjacent organs. For resection of advanced carcinoma an aggressive approach is required, but it has yet to be determined whether radical surgery can improve the outcome. Donohue *et al.*[3] reported that radical cholecystectomy failed to improve survival rates compared with cholecystectomy alone. Others have also reported radical surgery including wedge resection of the liver and resection of the supraduodenal common bile duct and draining satellite nodes, but for only 5–7 per cent of patients, with a poor prognosis[16–18]. Nakamura *et al.*[8] reported that two of 13 patients with advanced gallbladder carcinoma undergoing extended liver resection were alive at 5 years, a higher survival rate than for non-resected cases. Nimura *et al.*[9] reported that hepatic resection with pancreaticoduodenectomy in 14 patients achieved a median survival of 12·4 months and two alive at 2-years. Radical surgical treatment carries a high incidence of morbidity and mortality[9,10].

In the present study 44 patients with advanced gallbladder carcinoma of stage pT_3 and pT_4 had aggressive resection to obtain a 'curative' resection. Operation included extended hepatic resection, bile duct resection, colonic and gastroduodenal resection, and pancreaticoduodenectomy. Only 23 patients had a potentially curative resection despite the radical surgery. Prognosis was very poor in the 21 patients who had non-curative resection:

two were alive at 1 year and none at 2 years after surgery. A satisfactory survival rate of four and two of 23 patients at 3 and 5 years respectively followed curative resection. The aim of this study was to determine which patients were likely to benefit from radical surgery. A classification for advanced gallbladder carcinoma was used. Most patients with advanced gallbladder carcinoma were classified as having either type I (15 patients) or type III (26) disease. There were few patients with type II or IV involvement in this study. Patients with type I tumours, including infiltration into the liver with or without gastrointestinal invasion but not into the bile duct, had the best chance of curative resection in this study. Patients with type III disease, in whom the tumour had infiltrated both the liver and bile duct with or without gastrointestinal invasion, had little chance of curative resection. Operative procedures were not significantly different between patients with type I and III tumours, except portal vein resection which was performed in only six patients with type III disease. This suggests that portal vein resection alone does not contribute to curative resection or improved outcome.

Surgical morbidity and mortality rates were 20 of 44 patients and nine of 44 respectively, which emphasizes the operative stress of radical surgery and is similar to previous reports[9,10]. The surgical mortality rate was lower in patients with type I tumours (two of 15 patients) than in those with type III involvement (seven of 26). Postoperative survival following curative resection was significantly better in patients with type I tumours (four and two of 14 patients at 3 and 5 years respectively).

This classification of advanced gallbladder carcinoma according to the involvement of adjacent organs is helpful in choosing patients for whom an extended surgical approach might improve prognosis. Patients with advanced gallbladder carcinoma of type I, in which tumour infiltrates mainly into the liver but not into the bile duct, have the best chance of improved outcome with low morbidity and mortality rates after radical surgery.

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Hepatic bile acid synthesis and DNA synthetic rate after partial hepatectomy

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The relationship between hepatic DNA synthetic rate and activity of cholesterol 7α-hydroxylase, the rate limiting enzyme for bile acid synthesis, was examined in regenerating liver after partial hepatectomy or sham operation in rats. Hepatic cholesterol 7α-hydroxylase activity was significantly ($P<0.001$) suppressed on days 1 and 2, returned to the control level on day 3, and was significantly raised on day 7 after hepatectomy. The rate of DNA synthesis was significantly ($P<0.001$) activated during the first 3 days after hepatectomy and returned to the control level on day 7. Enzyme activities regulating hepatic bile acid synthesis and DNA synthesis change inversely during liver regeneration after hepatectomy.

Regeneration of the liver following partial hepatectomy occurs in both animals and humans[1–3], but differences exist in liver regeneration between cirrhotic and normal liver[4]. Bile secretion is an important function of the liver and biliary phospholipid and cholesterol secretion are induced by bile acid secretion from hepatocytes[5].

Hepatectomy may alter the hepatic bile acid synthetic rate, but there is little information concerning the effects of liver regeneration on bile acid synthesis. Recently, Xu *et al.*[6] reported that the bile acid synthetic rate correlated with the mass of the regenerating liver after hepatectomy by measuring biliary lipid secretion in rats after biliary diversion. However, biliary diversion itself affects bile acid synthesis[7]. The activity of hepatic cholesterol 7α-hydroxylase, the rate limiting enzyme converting cholesterol to bile acid, may be suppressed shortly after hepatectomy because the hepatocyte requires cholesterol for regeneration[8].

The detailed relationship between cholesterol 7α-hydroxylase activity and rate of DNA synthesis during liver regeneration has not been studied previously. Such an investigation was therefore undertaken in rats after 70 per cent hepatectomy without biliary diversion.

Materials and methods

Reagents

5α-Cholestane-3β, 7β-diol and 7α-hydroxycholesterol were synthesized as described previously[9]. TMSI-H (hexamethyldisilazane-trimethylchlorosilane-pyridine, 2:1:10) was from Gasukuro Kogyo (Tokyo, Japan). Ethylenediamine tetra-acetic acid (EDTA) and dithiothreitol (DTT) were from Sigma Chemical Company (St Louis, Missouri, USA) and the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) from Kojin (Tokyo, Japan). Bond-Elut silica cartridge columns (bonded phase, SI; size 3 ml) were from Analytichem International (Harbor City, California, USA).

Experimental protocol

Eight-week-old male Wistar rats weighing 250–300 g (Kyudo, Saga, Japan) were acclimatized to the animal room at a controlled temperature of 21°C for 1 week They had free access to food and water throughout the experiment. Rats were randomly divided into two groups and underwent either 70 per cent hepatectomy or sham operation according to techniques previously described[4,10]. The weight of the excised liver was recorded. Rats were killed on the day before or on days 1, 2, 3 and 7 after operation. For measurement of DNA synthetic rate tritiated thymidine (specific activity 42 Ci/mmol; Amersham International, Amersham, UK) 0·4 μCi per g body-weight was injected intraperitoneally 1 h before killing.

Assay of cholesterol 7α-hydroxylase activity

Hepatic microsomal cholesterol 7α-hydroxylase activity was determined by the method of Yamashita *et al.*[9]. Liver homogenate (10 per cent w/v) was prepared in Tris-HCl buffer (pH 7·4) 50 mol/l containing sucrose 0·3 mol/l, EDTA 10 mmol/l and DTT 10 mmol/l. The microsomal fraction was obtained by the method of Reihner *et al*[11], and an aliquot was used for determination of protein concentration[12]. The assay system consisted of 0·5 ml microsomal fraction containing 0·25–1·0 mg protein, phosphate buffer (pH 7·4) 0·1 mol/l, EDTA 1 mmol/l and NADPH 1 mmol/l in a total volume of 1·0 ml. The enzyme reaction was terminated after 15 min at 37°C by adding 10 ml chloroform/methanol (2/1 v/v). 5α-Cholestane-3β, 7β-diol (200 pmol dissolved in 50 μl of ethanol) was added as an internal standard. The sample was purified on a Bond-Elut silica cartridge column, derivatized to trimethylsilyl ether, and 7α-hydroxycholesterol was quantified by gas–liquid chromatography-selected ion monitoring mass spectrometry. The amount of 7α-hydroxycholesterol formed in the 15-min incubation period was calculated; cholesterol 7α-hydroxylase activity was expressed as pmol per min per mg microsomal protein and pmol per min per g liver.

Measurement of DNA synthetic rate

The liver was washed with cold physiological saline through the hepatic vein. The DNA fraction was extracted and the incorporation of [^{3}H]thymidine into DNA was determined as described elsewhere[13–15]. The DNA synthetic rate was expressed as d.p.m. per μg DNA.

Statistical analysis

Data are expressed as mean(s.e.m.) or median (95 per cent confidence interval). Statistical significance was calculated using the Wilcoxon–Mann–Whitney test for non-parametric comparison, and probability values of less than 0·01 were considered significant.

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Results

The body-weight of the rats, liver weight and the serum glutamic oxaloacetic transaminase level before and after hepatectomy are shown in *Table 1*. Liver weight increased depending on the time after hepatectomy and the remaining liver weight per 100 g body-weight recovered by 82 per cent of the control value by day 7 after hepatectomy. The serum glutamic oxaloacetic transaminase level was significantly raised for 3 days after hepatectomy it was maximal on the first day and returned to the basal control value by day 7 after hepatectomy.

The mean(s.e.m.) concentrations of DNA in the liver before and on days 1, 2, 3 and 7 after hepatectomy were 2·9(0·3), 2·8(0·2), 3·2(0·3), 3·3(0·2) and 3·4(0·3) mg per g liver respectively. The respective mean(s.e.m.) concentrations of hepatic microsomal protein were 13·3(0·7), 12·5(0·8), 13·1(1·1), 12·4(0·8) and 13·8(1·4) mg per g liver. These values were essentially similar to control values and were constant throughout the experiment. No significant difference was found.

Table 1 Body-weight, liver weight and serum liver function test before and after 70 per cent hepatectomy

	Body-weight (g)	Liver weight per 100 g body-weight	Glutamic oxaloacetic transaminase (units/l)
Hepatectomy group			
Before hepatectomy ($n=8$)	295(6)	4·2(0·1)	83(8)
After hepatectomy			
Day 1 ($n=8$)	263(6)	2·0(0·1)	1210(192)
Day 2 ($n=8$)	279(7)	2·7(0·2)	450(32)
Day 3 ($n=8$)	260(9)	2·9(0·1)	164(15)
Day 7 ($n=8$)	265(8)	3·2(0·3)	92(12)
Control group			
Before sham surgery ($n=6$)	294(6)	4·1(0·1)	90(9)
After surgery			
Day 1 ($n=6$)	276(4)	3·9(0·3)	420(60)
Day 2 ($n=6$)	278(5)	4·2(0·2)	130(18)
Day 3 ($n=6$)	278(5)	4·1(0·1)	92(12)
Day 7 ($n=6$)	299(7)	3·9(0·2)	85(7)

Values are mean(s.e.m.)

Cholesterol 7α-hydroxylase activities and DNA synthetic rates are shown in *Table 2*. The activity expressed as pmol per min per mg microsomal protein declined to one-fifth of preoperative levels on day 1 after 70 per cent

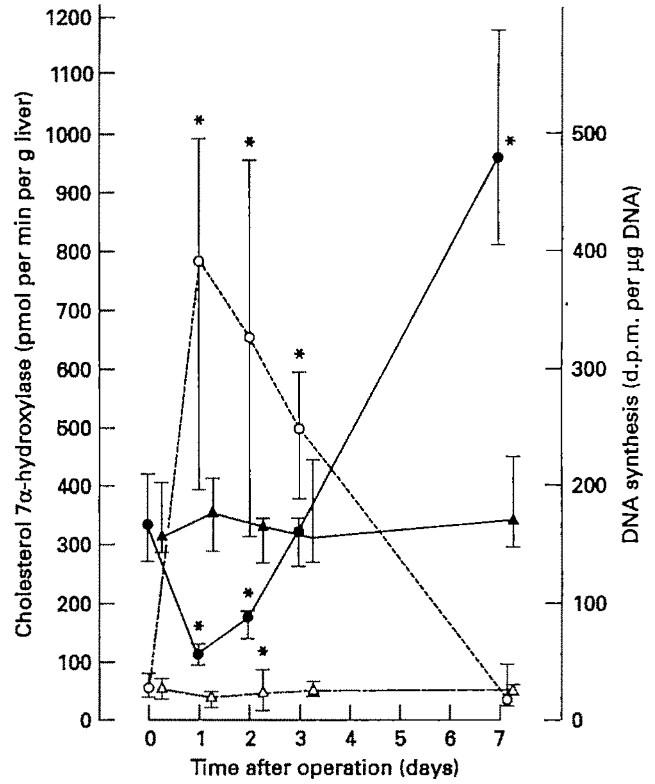

Fig. 1 Hepatic DNA synthesis rate (○, 70 per cent hepatectomy group, △, sham-operated group) and cholesterol 7α-hydroxylase activity (●, 70 per cent hepatectomy group; ▲, sham-operated group) on days 0, 1, 2, 3 and 7 after sham operation or 70 per cent hepatectomy. Values are median (95 per cent confidence interval), $n = 8$ in the hepatectomy group and $n = 6$ in the control group. Reciprocal changes in cholesterol 7α-hydroxylase activity and rate of DNA synthesis are evident after hepatectomy, but no changes are observed in the sham-operated group $^*P<0·01$ *versus* sham-operated group (Wilcoxon–Mann–Whitney test)

Table 2 Rate of DNA synthesis and cholesterol 7α-hydroxylase activity before and after hepatectomy

		Time after surgery (days)			
	Before surgery	1	2	3	7
Hepatectomy group					
Cholesterol 7α-hydroxylase (pmol per min per mg protein)	28·7 (16·2–33·8)	5·9 (3·9–7·3)*	12·7 (6·5–21·2)†	29·2 (19·5–30·9)	65·7 (51·5–95·4)*
Cholesterol 7α-hydroxylase (pmol per min per g liver)	336 (271–423)	112 (97–131)*	178 (141–189)*	327 (264–346)	963 (815–1176)*
DNA synthesis (d.p.m. per μg DNA)	28·6 (20·6–40·9)	392 (197–495)*	329 (158–477)*	250 (190–299)*	18·1 (14·3–48·5)
Control group					
Cholesterol 7α-hydroxylase (pmol per min per mg protein)	31·1 (24·8–32·8)	31·2 (24·1–31·8)	25·4 (20·1–29·3)	29·5 (24·0–32·8)	32·2 (25·8–34·8)
Cholesterol 7α-hydroxylase (pmol per min per g liver)	317 (289–408)	356 (290–415)	332 (270–346)	315 (270–448)	347 (299–453)
DNA synthesis (d.p.m. per μg DNA)	28·6 (18·5–35·5)	21·0 (12·3–24·9)	23·6 (9·1–42·6)	26·2 (21·3–33·9)	28·2 (23·2–30·5)

Values are median (95 per cent confidence interval), $n=8$ in the hepatectomy group and $n=6$ in the sham-operated control group. $^*P<0·001$, $^\dagger P<0·008$ *versus* corresponding control value (Wilcoxon–Mann–Whitney test) hepatectomy, to half on day 2, and returned to the control level on the third day. The enzyme activity thereafter increased to twofold that of the corresponding control value on the seventh postoperative day. Thus, there was a significant decrease ($P < 0\cdot001$) in the activity during the first 2 days and a significant increase ($P < 0\cdot001$) on day 7 after hepatectomy compared with control values (*Table 2*). The activity per gram of liver showed essentially similar changes after hepatectomy.

Incorporation of [^{3}H]thymidine into DNA was significantly increased during the first 3 days after hepatectomy and returned to the control level by day 7 (*Table 2*). Both the cholesterol 7α-hydroxylase activity and DNA synthetic rate in the sham-operated control group were constant and no significant change was observed during the observation period.

The DNA synthetic rates and activities of cholesterol 7α-hydroxylase before and after hepatectomy are depicted in *Fig. 1*, from which it can be seen that the rate of DNA synthesis changed inversely to the cholesterol 7α-hydroxylase activity during liver regeneration.

Discussion

The present study shows an inverse relationship between the rate of DNA synthesis and the activity of cholesterol 7α-hydroxylase in regenerating liver. Suppression of hepatic cholesterol 7α-hydroxylase activity during the activation of hepatocyte proliferation (DNA synthesis) was evident. The results suggest that the enzyme activity for bile acid synthesis may be suppressed because of the increased demand of cholesterol for hepatocyte proliferation after hepatectomy.

There is very limited knowledge of bile acid metabolism in the regenerating liver. Recently, Xu *et al.*[6] demonstrated that the bile acid synthetic rate depended on the mass of the regenerating liver after hepatectomy in the rat with bile diversion. If the rate of bile acid synthesis merely depended on liver mass, the activity of cholesterol 7α-hydroxylase (pmol per min per g liver) should remain constant. However, the activity was significantly suppressed for the first 2 days after hepatectomy, returned to the control level on the third day and increased thereafter, while the liver weight increased progressively in the week after operation. The reason for the discrepancy between the present results and those of Xu *et al.*[6] might be methodological. Xu and colleagues calculated the bile acid synthetic rate from the biliary bile acid secretion. Since biliary diversion influences the rate of bile acid synthesis[7], the authors suggest that the present model is more physiological because of the absence of biliary diversion. In the present study, loss of bile acids in the resected liver lobes was negligible because the bile acid component in the resected portion of the liver corresponded to less than 2 per cent of the total bile acid pool in the body[16]. Although a close relationship has been shown to exist between the serum 7α-hydroxycholesterol level, a possible parameter of hepatic cholesterol 7α-hydroxylase activity, and biliary bile acid secretion in patients with obstructive jaundice[17], the direct relationship between cholesterol 7α-hydroxylase activity and bile acid secretion into bile is unknown.

Cholesterol is an essential constituent of biological membranes and a precursor of bile acids and steroid hormones. Field *et al.*[8] reported that the activity of 3-hydroxy-3-methyl-glutaryl CoA (HMG-CoA) reductase, the rate limiting enzyme of cholesterol synthesis, was increased 12 h after hepatectomy and was maintained at a higher level for 72 h, while an increase in cholesterol synthesis was not observed until 48 h after partial hepatectomy. Cholesterol synthesis, as assessed by tritiated water incorporation into cholesterol, was significantly activated 48 and 72 h after hepatectomy. It was concluded that new cholesterol synthesis was not necessary for the initiation of DNA synthesis, but was required for continued hypertrophy and hyperplasia of the regenerating liver. It was also suggested that the supply of existing cholesterol was no longer sufficient 48 h after hepatectomy to meet the demands of hepatic regeneration. Decreased cholesterol 7α-hydroxylase activity of the regenerating liver at an early stage might be due to excessive use of cholesterol for hepatocyte proliferation and a decreased cholesterol pool available to cholesterol 7α-hydroxylase. Hepatic energy and cholesterol are primarily consumed for cell proliferation during this period[8,18,19].

The decreased cholesterol 7α-hydroxylase activity and increased DNA synthesis observed in the present study suggest that cell proliferation has priority over bile acid synthesis during the early stage of liver regeneration. Since HMG-CoA reductase is activated shortly after hepatectomy[8], dissociation between the two enzyme activities regulating hepatic cholesterol synthesis and bile acid synthesis may take place during this period. Dissociation of the two enzyme activities has been reported in other conditions[20,21], but the mechanism regulating these two enzymes may be more complicated in the regenerating liver. Within a few hours after hepatectomy, levels of hepatocyte growth factor increase and it binds to the c-met receptor on hepatocytes to initiate DNA synthesis. This is followed by expression of proto-oncogenes, nuclear division, cellular hypertrophy and hyperplasia[22]. How these events relate to regulation of the successive changes of cholesterol and bile acid synthetic pathways requires further study.

The significantly higher cholesterol 7α-hydroxylase activity on day 7 after hepatectomy may be a rebound phenomenon in response to the decreased rate of bile acid synthesis and/or bile acid pool size. Significant reduction of the bile salt pool size on days 3 and 7 after hepatectomy has been reported in rats[6,23].

In conclusion, hepatic cholesterol 7α-hydroxylase activity is suppressed during the period of activated DNA synthesis shortly after hepatectomy. The rate of DNA synthesis correlates inversely with bile acid synthesizing enzyme activity.

Acknowledgements

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Editor's announcement

Illustrations in colour

The Journal does not contain many illustrations in colour at present, probably because authors are usually requested to make a contribution towards the cost of colour reproduction. This cost is substantial, amounting to approximately £500 per figure at current rates. In association with the publishers, Blackwell Science Ltd, The British Journal of Surgery Society is keen to increase the number of colour illustrations in the Journal. The use of colour is particularly appropriate for operative photographs (whether open operation or laparoscopy), resection specimens and especially photomicrographs. To encourage the submission of suitable illustrations in colour, authors' charges will be waived. Three high-quality prints of each figure should be submitted.

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Effect of terminal ileal transposition on intestinal absorption following proctocolectomy

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A terminal ileal transposition procedure, in which a distal jejunal segment is interposed between the terminal ileum and the anus following proctocolectomy, is described. Adult mongrel dogs had either terminal ileal transposition ($n = 5$) or ileoanal anastomosis ($n = 6$) following two-stage proctocolectomy. Untreated dogs were used as controls ($n = 7$). Twelve weeks after the second-stage operation, a perfusion study was performed. After terminal ileal transposition the transposed terminal ileum showed a high absorptive capability for sodium, chloride and bile acids ($P < 0{\cdot}05$, $P < 0{\cdot}05$ and $P < 0{\cdot}001$ respectively). After ileoanal anastomosis the absorptive capability of the terminal ileum was not enhanced significantly. In the mid-jejunum, the absorption of bile acids, chloride and glucose was enhanced (all $P < 0{\cdot}05$) only after terminal ileal transposition. Terminal ileal transposition improves the absorptive capability of the terminal ileum and the mid-jejunum compared with conventional ileoanal anastomosis in this model.

Ileal pouch–anal anastomosis has become the most commonly used reconstruction following proctocolectomy in patients with ulcerative colitis and familial adenomatous polyposis[1–3]. The technique produces a better quality of life than Brooke ileostomy or Kock's continent ileostomy[2–4]. A larger pouch is associated with a lower frequency of defaecation[4,5]. For this reason, various efforts have been made to create a larger pouch using the terminal ileum, such as the J, S, W and isoperistaltic lateral pouches[6–8].

The terminal ileum is the only site that actively absorbs bile acids and vitamin B_{12}. This portion of the small intestine is also known to be an important site in regulating gastrointestinal motility, termed the 'ileal brake', and in releasing certain gut hormones such as peptide YY and enteroglucagon[9]. When the terminal ileum is used, stasis of faeces in the pouch causes chronic inflammation or bacterial overgrowth[10–12] which leads to malabsorption of glucose, sodium, carbohydrates, amino acids and short-chain fatty acids[10–15]. The specific function of the terminal ileum, including active absorption of bile acids and vitamin B_{12}, is also impaired[13–15]. Bile acid malabsorption is one of the reasons for steatorrhoea after proctocolectomy and J pouch–anal anastomosis[15]. Moreover, severe acute inflammation, known as 'pouchitis', can be a serious problem[16–18]. Once pouchitis occurs, the morphological structure of the terminal ileum is damaged by acute inflammatory changes, such as ulceration and severe inflammatory cell infiltration[16–18].

Surgeons face a dilemma about the creation of the ideal ileal pouch because a larger pouch reduces the frequency of defaecation but impairs the special function of the terminal ileum[4,5,14]. Stelzner *et al.*[14] concluded that a small pouch is the preferred option to preserve terminal ileal function. No operative procedure has yet been devised to spare the terminal ileum.

The authors have designed a terminal ileal transposition procedure in which a distal jejunal segment is interposed between the terminal ileum and the anus to function as a neocolon. The terminal ileum is located apart from the anus and is not used as a reservoir. The advantages of this procedure in preserving the absorptive capability and morphology of the terminal ileum in an experimental animal model have been reported previously[19–22]. The purpose of this study was to investigate the effect of the terminal ileal transposition procedure on the absorptive capability of the small intestine, especially that of the terminal ileum, and to compare the procedure with conventional ileoanal anastomosis following proctocolectomy.

Materials and methods

Operative procedures

Adult mongrel dogs weighing 10–15 kg were maintained in a normal laboratory environment on standard chow for at least 2 weeks before the study. Animals were randomly assigned to either terminal ileal transposition ($n = 5$) or ileoanal anastomosis ($n = 6$) and deprived of food, but not water, for 12 h before surgery. The dogs had a two-stage proctocolectomy under intravenous anaesthesia with sodium pentobarbital 25 mg/kg. The second stage was performed 5 weeks after the first operation. Dogs were given 500 ml lactated Ringer's solution via a central venous catheter during the operation. The details of the surgical procedure have been reported previously[19–22]. The animals were given 500 ml lactated Ringer's solution and cefuzonum sodium (Cosmosin; Takeda, Tokyo, Japan) 500 mg daily via a central venous catheter for 3 days after each stage.

Terminal ileal transposition (Fig. 1). In the first stage, distal colectomy and proctectomy were performed. A 40–50-cm segment of lower jejunum on a vascular pedicle, which originated 40–50 cm above the ileocaecal junction, was transposed between the remaining proximal colon and the anus above the dentate line as a neocolon. In the second-stage operation, the remaining colon was resected to complete the proctocolectomy. The distal end of the terminal ileum 1 cm proximal to the ileocaecal junction was anastomosed to the proximal end of the interposed jejunum. In this procedure, the terminal ileum was located 40–50 cm from the anus so it would not function as a neocolon.

Ileoanal anastomosis (Fig. 2). Distal colectomy and proctectomy were performed in the first-stage operation. A 40–50-cm segment of the terminal ileum on a vascular pedicle, located 1 cm proximal to the ileocaecal junction, was transposed between the proximal colon and the anus as a neocolon.

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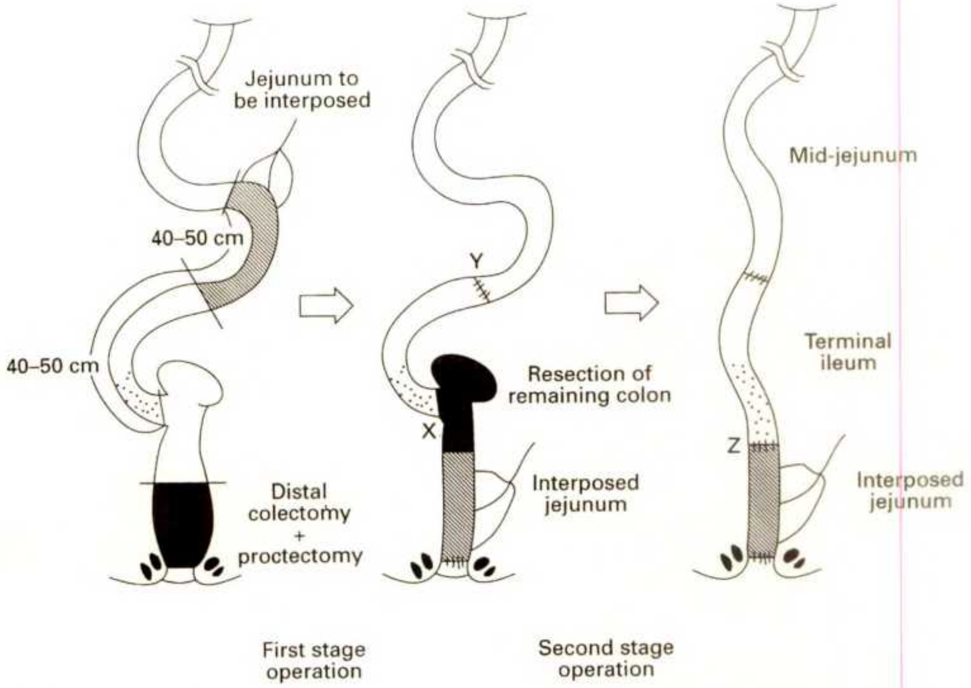


Fig. 1 Operative procedure for two-stage proctocolectomy including terminal ileal transposition. In the first stage, distal colectomy was performed and a jejunal segment was interposed as a neocolon. In the second stage, residual proximal colon was resected and anastomosis between the terminal ileum and interposed jejunum was performed. The terminal ileum was located apart from the anus. X, ileocaecal junction; Y, jejunojejunostomy; Z, ileojejunostomy

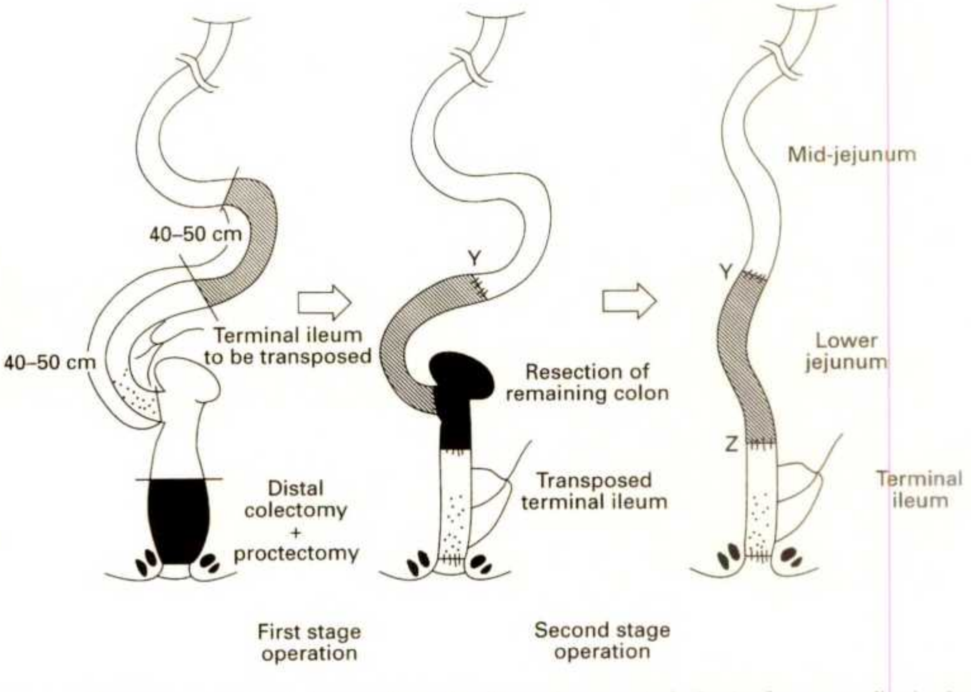

40–50 cm
40–50 cm
Terminal ileum to be transposed
Distal colectomy + proctectomy
Y
Resection of remaining colon
Transposed terminal ileum
Mid-jejunum
Y
Lower jejunum
Z
Terminal ileum
First stage operation
Second stage operation

Fig. 2 Operative procedure for two-stage proctocolectomy including ileoanal anastomosis. In the first stage, distal colectomy was performed and a terminal ileal segment was interposed as a neocolon. In the second stage, residual proximal colon was resected and jejunoileal anastomosis was performed. The terminal ileum was located just proximal to the anus as a neocolon. Y, seromuscular cutting; Z, jejunoileostomy

Seromuscular cutting and reanastomosis were performed on the lower jejunum 80–100 cm proximal to the ileocaecal junction to create the same number of anastomoses in the two groups after completion of the proctocolectomy. In the second-stage operation, the remaining colon was resected and the distal end of the lower jejunum was anastomosed to the proximal end of the ileum. In this procedure, the terminal ileum was anastomosed directly to the anus.

Control group. Untreated dogs were used as controls ($n = 7$). Dogs were kept under normal laboratory conditions for at least 2 weeks before absorption studies.

Perfusate preparation

The perfusate was made by diluting pooled canine gallbladder bile collected from 40 dogs who were used for other acute experiments after bile collection. These dogs had a laparotomy under general anaesthesia after overnight fasting. Gallbladder bile was collected by puncture aspiration using a 21-G needle, and refrigerated at −20°C. After collection of bile from 40 dogs, it was thawed, combined, homogenized and stirred. After division into aliquots, the bile was refrigerated at −20°C until use. Just before each absorption study, bile was thawed, homogenized, centrifuged at 50 000*g*, and diluted 20-fold with normal saline containing polyethylene glycol (PEG) 5 g/l and glucose 30 mmol/l. The final perfusate contained sodium 158 mmol/l, chloride 145 mmol/l, potassium 0·54 mmol/l, glucose 530 mg/dl and total bile acids 13·8 mmol/l.

Absorption studies

More than 12 weeks after the second-stage operation, an absorption study was carried out on each dog by the modified method reported previously[19]. In brief, each dog underwent laparotomy under general anaesthesia with pentobarbital 25 mg/kg after overnight fasting. Lactated Ringer's solution was given intravenously at the rate of 80 ml/h throughout the study. Three 20-cm bowel segments for perfusion were selected (*Fig. 3*). Segment A comprised mid-jejunum. Segment B was prereservoir bowel and comprised transposed terminal ileum in dogs who had terminal ileal transposition and distal jejunum in other animals. Segment C was neocolon, consisting of terminal ileum in controls and dogs who had ileoanal anastomosis, and interposed distal jejunum in those who had terminal ileal transposition.

A polyethylene tube with an internal diameter of 1·5 mm was inserted into the intestinal lumen from 3 cm proximal to the site of the 20-cm test segment for infusion, and another 5-mm tube from 3 cm distal to the site for collection. Each test segment was isolated by ligating only the intestinal tract with tapes while marginal vessels were preserved. Before the experiment, each segment was irrigated gently with 200–250 ml normal saline to cleanse the lumen, and then the abdomen was covered with plastic wrap. Normal saline at 38·0°C was perfused at 18 ml/h for 60 min, after which the perfusate of diluted canine gallbladder bile was instilled at 18 ml/h via the proximal tube. The perfusate was maintained at 38·0°C using a warmer during the perfusion. After a 90-min equilibration period, effluent fluid was collected from the distal tube for two 30-min periods. The concentration of total bile acids in the effluent was measured by the 3α-hydroxysteroid dehydrogenase method[23]. PEG concentration was analysed turbidimetrically by the method of Malawer and Powell[24]. The concentrations of sodium, chloride and glucose in the effluent were measured by a commercial laboratory (JML, Fukuoka, Japan) using standard methods. Net absorption rates of water, bile acids, glucose, sodium and chloride were calculated from changes in PEG concentration[25]. Data from the two 30-min intervals were averaged in each dog and the mean value was used as the absorptive capability of each segment.

Just before the induction of anaesthesia, venous blood samples were taken and some were centrifuged to separate the serum. Blood and serum were analysed for complete blood count, liver function, total protein, albumin and electrolytes.

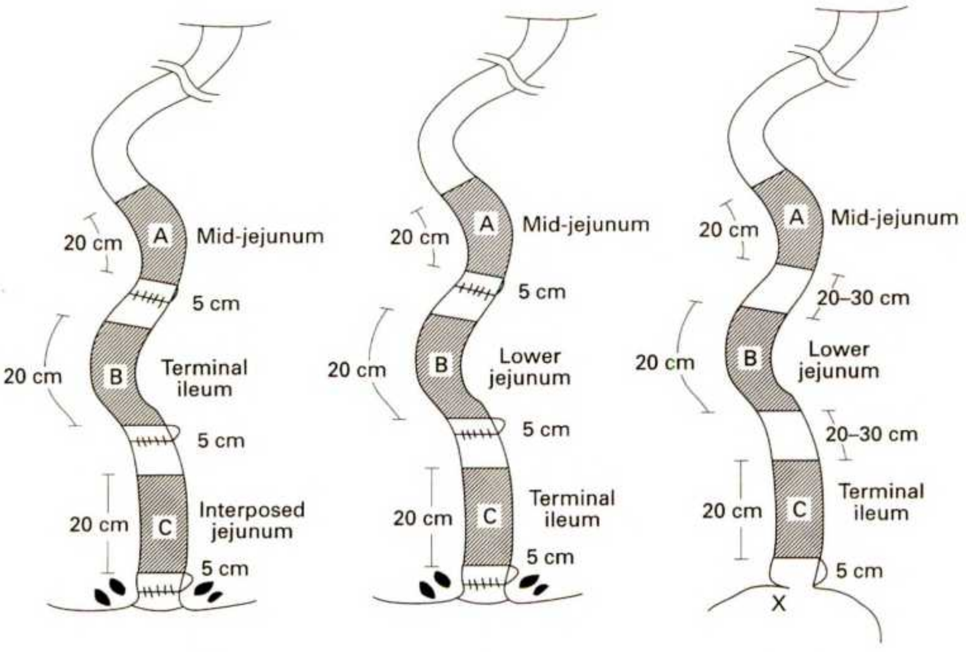
Statistical analysis

All data were expressed as mean(s.e.m.). Statistical comparison for significant differences between groups was performed with analysis of variance followed by Tukey's test. Statistical significance was accepted when $P < 0\cdot05$.

Results

General characteristics

In both groups of dogs who had surgery, diarrhoea occurred after the second-stage operation, but the stool gradually became semisolid after about 12 weeks. Most



Terminal ileal transposition

Ileoanal anastomosis

Control group

Fig. 3 Bowel segments for perfusion in absorption study. X, ileocaecal junction; A, mid-jejunum; B, prereservoir; C, neocolon

animals produced about ten stools per day; there was no difference in the frequency between the groups. As reported previously[19–22], moderate weight loss occurred at 6–8 weeks after the second-stage operation. However, dogs started to gain weight as the stool solidified. No significant difference was observed in weight loss between the groups.

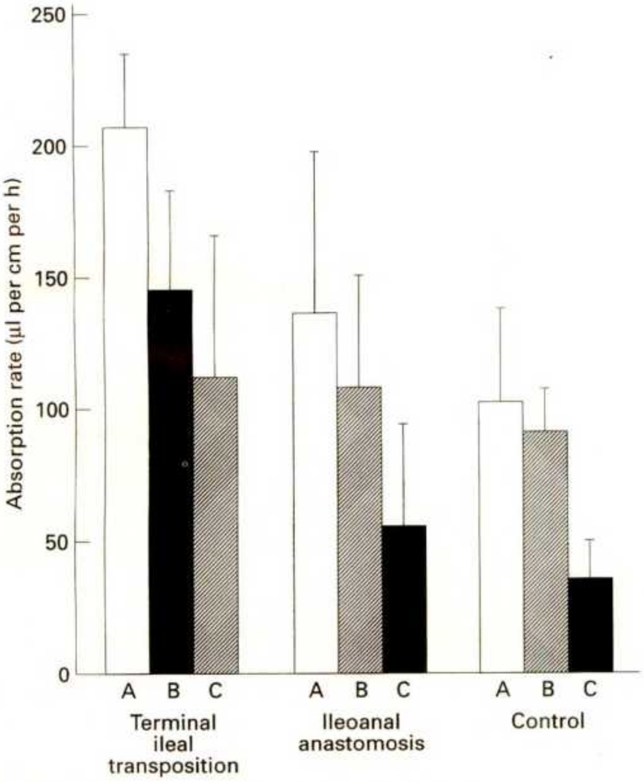


Fig. 4 Mean(s.e.m.) water absorption rate. There was no significant difference between the groups at any site. A, mid-jejunum; B, prereservoir; C, neocolon. ☐, Mid-jejunum; ▨, lower jejunum; ■, terminal ileum

Serum tests

Data summarizing the standard haematological indices, results of serum liver function tests and nutritional parameters are shown in *Table 1*. Anaemia was not

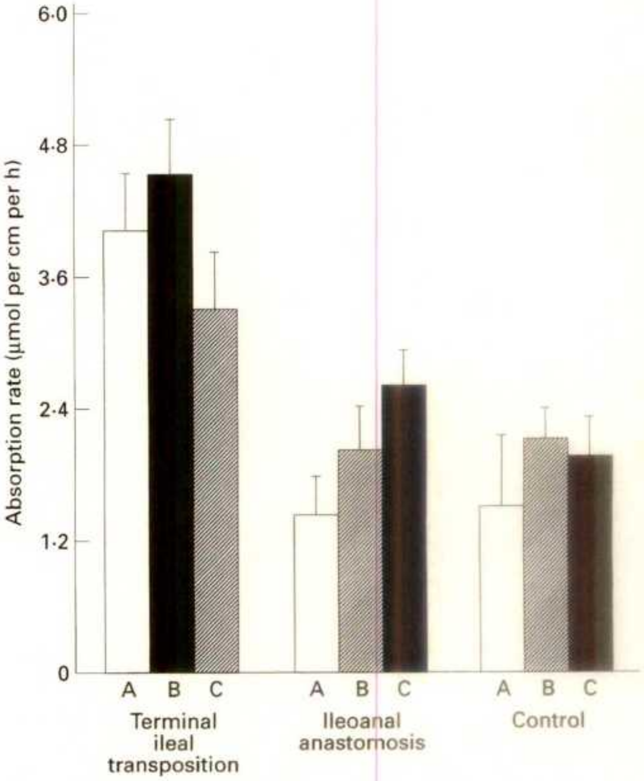


Fig. 5 Mean(s.e.m.) bile acid absorption rate. Absorption was enhanced in the terminal ileum after terminal ileal transposition *versus* ileoanal anastomosis ($P < 0·01$) and controls ($P < 0·001$). Bile acid absorption was also enhanced in the mid-jejunum after terminal ileal transposition *versus* ileoanal anastomosis ($P < 0·05$) and controls ($P < 0·05$). A, mid-jejunum; B, prereservoir; C, neocolon. ☐, Mid-jejunum; ▨, lower jejunum; ■, terminal ileum

Table 1 Effect of proctocolectomy on complete blood cell count and serum chemistry

	Terminal ileal transposition ($n = 5$)	Ileoanal anastomosis ($n = 6$)	Control ($n = 7$)
Red blood cells (× 10^4/mm^3)	550(68)	552(47)	528(67)
Haemoglobin (g/dl)	12·0(1·7)	12·5(1·0)	10·6(1·4)
Haematocrit (%)	36·0(4·6)	37·6(2·8)	33·8(4·0)
White blood cells (/mm^3)	10 800(1890)	9330(1670)	9890(790)
Total protein (g/dl)	5·5(0·3)	6·0(0·2)	6·2(0·1)
Albumin (g/dl)	2·6(0·2)	2·6(0·1)	3·0(0·2)
Cholesterol (mg/dl)	147(6)	161(19)	126(13)
Triglyceride (mg/dl)	35·2(1·9)	36·8(1·4)	32·4(6·0)
AST (units/l)	22·4(3·5)	18·3(0·9)	18·0(1·0)
ALT (units/l)	31·6(7·3)	20·8(2·5)	30·4(17·0)
ALP (units/l)	43·4(4·3)	84·7(17·9)	67·7(19·5)
Total bilirubin (mg/dl)	0·06(0·02)	0·08(0·02)	0·20(0·00)
Sodium (mmol/l)	141(4)	142(1)	144(1)
Potassium (mmol/l)	4·6(0·2)	4·3(0·2)	4·5(0·2)
Chloride (mmol/l)	110(3)	113(1)	109(1)
Calcium (mg/dl)	9·4(0·4)	9·2(0·3)	10·3(0·4)

Values are mean(s.e.m.). AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase

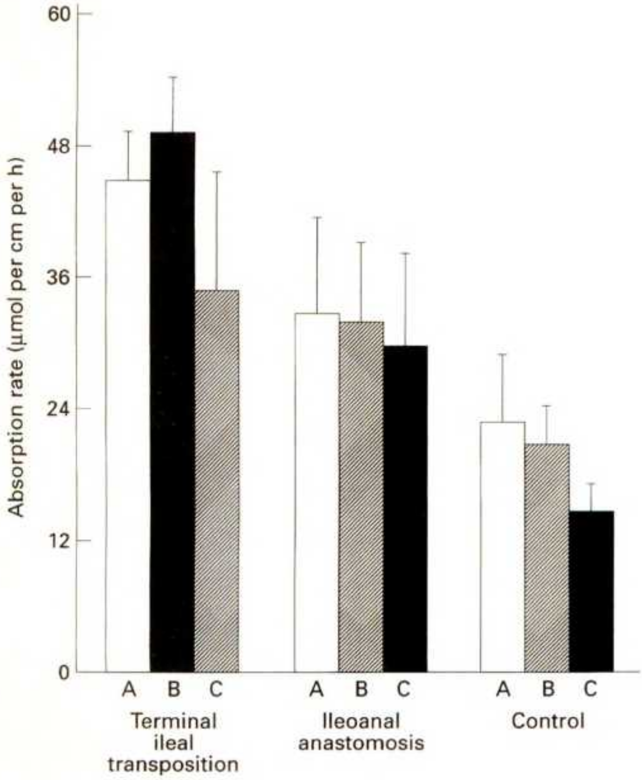


Fig. 6 Mean(s.e.m.) sodium absorption rate. There was a significant difference in the absorption rate of sodium in the terminal ileum between dogs who had terminal ileal transposition and controls ($P < 0{\cdot}01$). A, mid-jejunum; B: prereservoir; C, neocolon. □, Mid-jejunum; ▨, lower jejunum; ■, terminal ileum

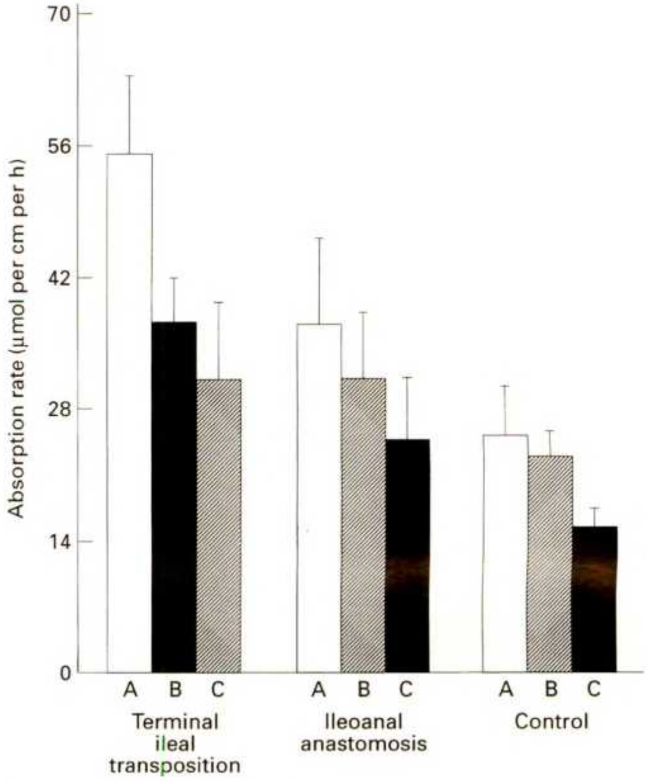


Fig. 7 Mean(s.e.m.) chloride absorption rate. In the terminal ileum, there was a significant difference in the chloride absorption rate between dogs who had terminal ileal transposition and controls ($P < 0{\cdot}05$). Mid-jejunum showed a higher absorption rate for chloride after terminal ileal transposition than controls ($P < 0{\cdot}05$). A, mid-jejunum; B, prereservoir; C, neocolon. □, Mid-jejunum; ▨, lower jejunum; ■, terminal ileum

observed in any group. Serum cholesterol, total protein, albumin and electrolyte levels were similar in all groups. Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and total bilirubin levels were within the normal range in each group and no differences were observed.

Absorption studies

Water absorption was enhanced in the mid-jejunum and the transposed terminal ileum in the dogs who had terminal ileal transposition. However, there was no significant difference between the groups at any site (*Fig. 4*). After terminal ileal transposition bile acid absorption was enhanced in the terminal ileum (mean(s.e.m.) 4·51(0·52) μmol per cm per h) compared with that after ileoanal anastomosis (2·59(0·33) μmol per cm per h; $P < 0{\cdot}01$) and in controls (1·93(0·37) μmol per cm per h; $P < 0{\cdot}001$) (*Fig. 5*). Bile acid absorption was also enhanced in the mid-jejunum after terminal ileal transposition (mean(s.e.m.) 4·01(0·52) μmol per cm per h) compared with that after ileoanal anastomosis (1·41(0·37) μmol per cm per h; $P < 0{\cdot}05$) and in controls (1·49(0·65) μmol per cm per h; $P < 0{\cdot}05$). The transposed terminal ileum showed high absorption rates for sodium (mean(s.e.m.) 49·1(5·0) μmol per cm per h) and chloride (37·1(5·0) μmol per cm per h) after terminal ileal transposition compared with the terminal ileum in the control group (14·3(2·6) μmol per cm per h ($P < 0{\cdot}01$) and 15·4(2·0) μmol per cm per h ($P < 0{\cdot}05$) respectively) (*Figs 6* and *7*). When the terminal ileum was used as a neocolon in dogs who had ileoanal anastomosis, the absorptive capability for bile acids, glucose, sodium and chloride of this segment was not enhanced significantly. In the mid-jejunum, chloride and glucose absorption rates were increased significantly (mean(s.e.m. 55·1(8·4) μmol per cm per h and 2·93(0·34) mg per cm per h respectively) after terminal ileal transposition compared with those in controls (25·1(5·3) μmol per cm per h ($P < 0{\cdot}05$) and 1·59(0·37) mg per cm per h ($P < 0{\cdot}05$) respectively) (*Figs 7* and *8*). Bile acid, sodium, chloride and glucose absorption rates showed no significant change in the mid-jejunum after ileoanal anastomosis compared with those in the mid-jejunum in controls.

Discussion

The present study has shown that terminal ileal transposition increases the absorptive capability of bile acids, sodium and chloride in the terminal ileum. However, when the terminal ileum is used as a neocolon when ileoanal anastomosis is performed, the absorptive capability of this segment is not enhanced significantly. The absorptive capability for bile acids, chloride and glucose was enhanced in the mid-jejunum compared with

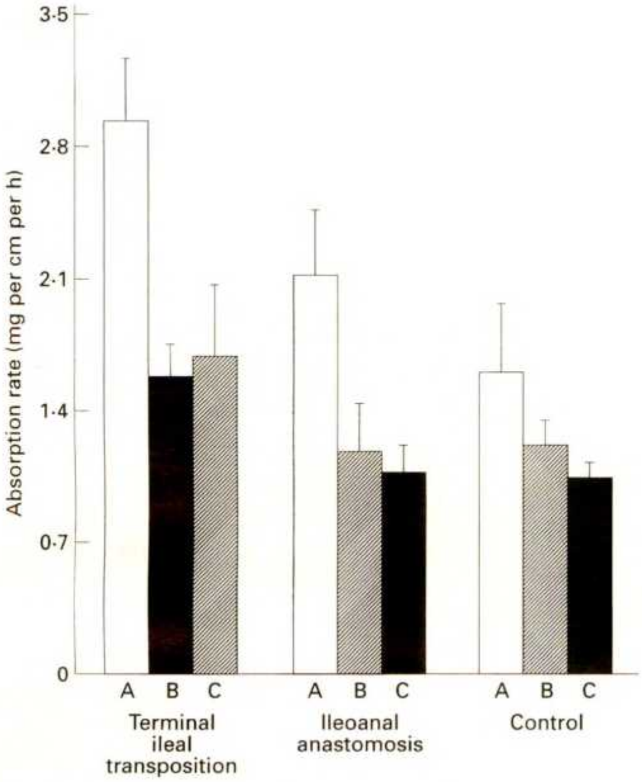


Fig. 8 Mean(s.e.m.) glucose absorption rate. Mid-jejunum showed a higher absorption rate for glucose in the terminal ileal transposition group than controls ($P < 0.05$). A, mid-jejunum; B, prereservoir; C, neocolon. □, Mid-jejunum; ▨, lower jejunum; ■, terminal ileum

that in controls after terminal ileal transposition only and not after ileoanal anastomosis.

As a surgical treatment for ulcerative colitis and familial adenomatous polyposis, proctocolectomy and ileoanal or ileal pouch–anal anastomosis is now widely accepted and has been shown to have clinical benefits[26–28]. However, the terminal ileum is exposed to acute and chronic inflammation when it is used as a reservoir[10–12,16–18]. This leads to an impaired absorptive function of the terminal ileum, especially for bile acids and vitamin B_{12}[10–15].

Although many variations have been proposed for the design and technique of creating a pouch using the terminal ileum[4–8], little attention has been given to avoiding the use of the terminal ileum as a reservoir. The terminal ileal transposition procedure was based on the concept of sparing the terminal ileum from being used as a neocolon. The advantages of this method in preserving the absorptive function and morphological structure of the terminal ileum following proctocolectomy have been reported[19–22]. This procedure does not decrease the ratio of secondary bile acids in the gallbladder bile[29]. The absorption of water and electrolytes is enhanced in the transposed terminal ileum but not in the interposed jejunum[19]. The largest increase in sodium–potassium adenosine 5'-triphosphatase activity and potential difference is found in the transposed terminal ileum compared with mid-jejunum and interposed jejunum[20]. In the present study, it has been shown that the transposed terminal ileum is superior in preserving and enhancing the absorptive capability of bile acids, sodium and chloride compared with conventional ileoanal anastomosis. It was shown previously that morphological changes in the transposed terminal ileal segment were reduced by this procedure[22], which may contribute to the enhanced absorptive capability.

The reason for the enhanced absorption of bile acids, chloride and glucose in the mid-jejunum after terminal ileal transposition is unclear. The terminal ileum is known to be an important site for the release of certain gut hormones, such as peptide YY, enteroglucagon and neurotensin[30]. In a recent report, Ohtani *et al.*[31] demonstrated that plasma peptide YY and enteroglucagon levels were increased and gastric motility was inhibited after ileojejunal transposition in dogs. Although the colon was not resected in their procedure, the terminal ileum was transposed into the proximal portion of the small intestine. Protection of the terminal ileum from acute and chronic inflammation using the terminal ileal transposition procedure may enhance the capability of releasing peptide YY and enteroglucagon more than conventional ileoanal anastomosis; however, this has not yet been investigated. Peptide YY increases the small bowel absorption of water and electrolytes[32]. Enteroglucagon is considered to be trophic to small intestinal mucosa, but peptide YY is not[33,34]. These hormones may play an important role in enhancing the absorptive capability of the mid-jejunum after terminal ileal transposition. Another report showed that mucosal weight and DNA content of the duodenum was increased after ileojejunal transposition[35]. Terminal ileal transposition may have had the same effect on the mid-jejunum as ileojejunal transposition had on the duodenum.

Not only does the terminal ileum have a special absorptive function but it has been reported to play an important role in the regulation of gastrointestinal motility, termed the 'ileal brake'[9]. Peptide YY is considered to be an important mediator of this phenomenon[9]. Gastric motility is inhibited after ileojejunal transposition in dogs[31]. Nakahara *et al.*[36] demonstrated that the transit time from mouth to stoma was prolonged, but enterohepatic circulation of bile acids was preserved, after interposing an ileal segment between the terminal ileum and ileostomy in rats. Terminal ileal transposition may have the benefit of slowing gastrointestinal transit which would aid jejunal absorption, although this has yet to be confirmed.

In this study, a pouch was not created after proctocolectomy to exclude the effects of a pouch on mucosal absorption. Even if a pouch is required, interposition of a jejunal segment is simple. The additional anastomoses may be a disadvantage of this procedure. While interposition of the jejunal segment does not cause ischaemic changes or congestion[22], the effect of pouch construction with jejunum on its function is unknown. It is possible that protection of terminal ileal function could result in sacrifice of jejunal function, lessening the benefits of such a procedure.

Data from this study on dogs suggest that the terminal ileal transposition procedure might result in a better long-term nutritional result after proctocolectomy. However, body-weight loss and stool frequency were not different between the groups, despite the differences in intestinal absorption. This suggests that other factors must be of significant importance in determining overall clinical outcome. Changes in the absorption of other nutrients, such as fats and amino acids, may be important and remain to be investigated.

The extrapolation of this procedure to humans is still unclear. It will be necessary to show greater long-term clinical benefits of terminal ileal transposition in the animal model before it is attempted in humans. The increased surgical difficulty of performing terminal ileal transposition must first be shown to be outweighed by important long-term clinical and nutritional benefits.

Acknowledgements

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Nitric oxide and the rectoanal inhibitory reflex: retrograde neuronal tracing reveals a descending nitrergic rectoanal pathway in a guinea-pig model

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Nitric oxide has been implicated as the neurotransmitter mediating internal anal sphincter (IAS) relaxation during the rectoanal inhibitory reflex. However, there has been no direct demonstration of a nitrergic rectoanal neuronal pathway appropriate to mediating the reflex. This study combined retrograde neuronal tracing techniques with enzyme histochemistry in a guinea-pig model. Wheatgerm agglutinin conjugated to horseradish peroxidase was injected into the IAS. Transported tracer was demonstrated in neurones of the myenteric ganglia of the distal rectum and all labelled neurones showed co-localization with nitric oxide synthase as revealed by reduced nicotinamide adenine dinucleotide phosphate diaphorase histochemistry. *In vivo* anal canal manometry showed that the mean maximal resting pressure was 16 (8–20) cmH$_2$O and confirmed the presence of the rectoanal inhibitory reflex. *In vitro* organ bath studies showed that strips of IAS developed spontaneous myogenic tone and relaxed in response to intrinsic nerve stimulation. Addition of N_{ω}-nitro-L-arginine (L-NOArg) reduced the relaxant response in a dose-dependent fashion; the relaxant response was maximally reduced by a mean(s.e.m.) 35·2(3·8) per cent ($P < 0{\cdot}001$) at a concentration of 3×10^{-5} mol/l L-NOArg. This study provides direct anatomical evidence of a descending nitrergic rectoanal neuronal pathway in a guinea-pig model. *In vivo* anal manometry and *in vitro* organ bath studies provide additional evidence that this pathway is responsible for the inhibitory motor innervation of the rectoanal inhibitory reflex.

Rectal distension induces physiological relaxation of the internal anal sphincter (IAS), a response known as the rectoanal inhibitory reflex. This reflex may underly the ability to discriminate faeces, fluid and flatus as anorectal sampling allows the contents of the rectum to contact the sensitive epithelium of the upper anal canal and, as the rectum fills, may be involved in the initiation of defaecation. The reflex is mediated by intrinsic non-adrenergic non-cholinergic inhibitory neurones. Physiological evidence that nitric oxide is the neurotransmitter involved has been produced by recording the mechanical responses of opossum IAS *in vivo*[1] and of IAS tissue from several species, including human, *in vitro*[2–5]. Anatomical studies have demonstrated a subpopulation of enteric neurones containing the enzyme nitric oxide synthase with appropriate distribution and morphology to subserve inhibitory innervation[6,7]. However, there has been no direct demonstration of a nitrergic rectoanal neuronal pathway appropriate to mediating the rectoanal inhibitory reflex.

This study sought to demonstrate such a pathway in a guinea-pig model by combining the techniques of retrograde neuronal labelling and enzyme histochemistry, and to validate the putative pathway by demonstrating the presence of a rectoanal inhibitory reflex *in vivo* and by providing physiological evidence of nitrergic non-adrenergic non-cholinergic-mediated relaxation of guinea-pig IAS *in vitro*.

Materials and methods

Neuronal tracing studies

Preliminary anatomical studies demonstrated that the guinea-pig IAS lies directly beneath the mucocutaneous junction and comprises an obvious ring of circularly orientated smooth muscle about 2 mm long at the distal end of the mucularis layer (*Fig. 1*).

Neuronal tracing studies were performed in eight adult Dunkin–Hartley guinea-pigs of either sex (body-weight 500–650 g). Procedures were performed under general anaesthesia with Hypnorm 0·5 ml/kg (fentanyl citrate 0·315 mg/ml, fluanisone 10 mg/ml; Janssen Pharmaceuticals, Oxford, UK) and Hypnovel 0·5 ml/kg (midazolam 5 mg/ml; Roche, Welwyn Garden City, UK). Animals were placed supine and a small nasal speculum was used to identify the anal mucocutaneous junction. Injections of 10-µl 5 per cent wheatgerm agglutinin–horseradish peroxidase (WGA–HRP, $n = 6$; Sigma Chemicals, Poole, UK) or saline ($n = 2$) were made into the IAS by air pressure with a Hamilton syringe. The needle tip was left in place for at least 1 min before withdrawal to minimize tracer backflow into the needle track.

After a survival time of 24 h animals were killed by cervical dislocation and exsanguinated. The abdominal cavity was opened and the pubic symphysis was divided to gain rapid access to the pelvic viscera. The anal canal and rectum were removed *en bloc* and washed briefly in phosphate buffered saline (PBS). The caudal and perineal glands were removed to leave the gut tube, striated muscle external anal sphincter and some of the pelvic floor intact. The bowel was transected at the upper margin of the IAS, which corresponds with an obvious thickening of the gut tube. The anal canals were embedded as complete doughnuts of tissue in Tissue-Tek OCT compound (Raymond Lamb, London, UK) in aluminium foil moulds, snap-frozen in isopentane cooled with liquid nitrogen and stored at −70°C until further processing.

The rectum was opened along the mesenteric border, pinned flat on silicone elastomer in a Petri dish and fixed by immersion for 18 h in freshly prepared 4 per cent paraformaldehyde in phosphate buffer 0·1 mol/l (pH 7·4) at 4°C. Tissue was washed in

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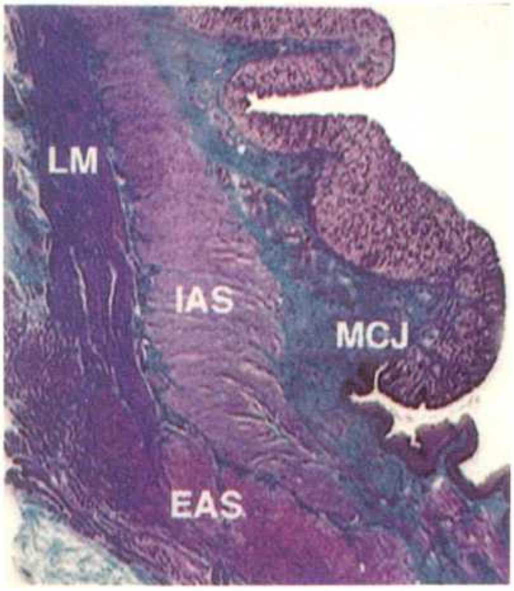

Fig. 1 Paraffin-embedded section of guinea-pig anal canal stained with Masson's trichrome (original magnification × 25). Internal anal sphincter (IAS) lies directly beneath mucocutaneous junction (MCJ). EAS, external anal sphincter; LM, longitudinal muscle

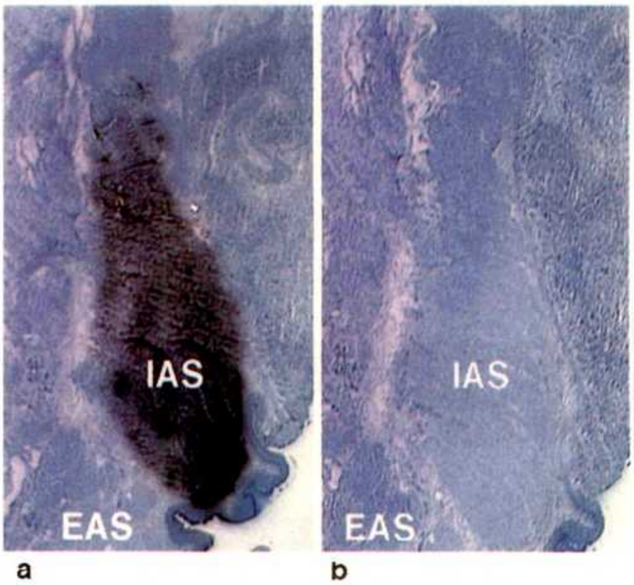

Fig. 2 a Cryostat section of anal canal reveals peroxidase activity confined to the internal anal sphincter (IAS) at the site of tracer injection. EAS, external anal sphincter. **b** No staining was seen in control sections. (Tetramethylbenzidine and haematoxylin; original magnification × 25)

PBS and whole mounts of the rectal longitudinal muscle and myenteric plexus were prepared with the aid of a dissecting microscope. Whole mounts were immediately processed as free-floating sections using a tetramethylbenzidine–molybdate method[8] to reveal HRP activity. Whole mounts were mounted in 0·3 per cent hypromellose on standard microscope slides, coverslipped and viewed by standard light microscopy with a Leitz Laborlux D microscope (Leica, Milton Keynes, UK). Areas of interest were photographed with an Olympus OM-4Ti SLR camera (Olympus Optical, London, UK) and a dedicated Leitz Periplan microscope–camera attachment (Leica, Milton Keynes, UK). The coverslips were removed and the whole mounts were processed again as free-floating sections using reduced nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase enzyme histochemistry before permanent mounting in aqueous mounting medium (Histotec; Serotec, Oxford, UK), further viewing and photography. Whole mounts were sufficiently robust to allow reliable orientation during these procedures.

Longitudinal sections ($10\,\mu m$) of anal canal specimens were cut in a cryostat at −23°C and mounted on Vectabond-treated slides (Vector Laboratories, Peterborough, UK). HRP activity at the injection site was revealed by the tetramethylbenzidine method. Sections were counterstained with haematoxylin, dehydrated (alcohol series), cleared and mounted for viewing and photography.

Demonstration of the rectoanal inhibitory reflex in vivo

Anal canal manometry was performed on six guinea-pigs by means of a station pull-through technique. Animals were sedated with Hypnovel 0·3 ml/kg and the anal canal pressure was measured at 1-mm intervals with a small-calibre single-channel pressure transducer (Gaeltec, Isle of Skye, UK). Measurements were calibrated in centimetres of water (cmH_2O) and recorded on a standard pen recorder. To test for the rectoanal inhibitory reflex, the pressure transducer was located at the level of maximal anal canal pressure and the balloon of a 4-Fr Pruitt–Nozick embolectomy catheter (Ideas for Medicine, Tampa, Florida, USA) was inflated to a diameter of 7 mm in the rectum 1 cm from the anal verge. Relaxation of 25 per cent or more from resting pressure was considered to represent a positive reflex.

In vitro *studies of guinea-pig internal anal sphincter*

Samples of isolated IAS were obtained from eight guinea-pigs, and strips were prepared for isometric tension recording in superfusion organ baths using methods reported previously[9]. Transmural electrical field stimulation of the intrinsic nerves was applied with square-wave impulses of 50 V, 0·05 ms duration, for 1 s at 4 Hz. Frequencies of 4 Hz or more elicited maximal responses in preliminary experiments. Control responses to electrical field stimulation were obtained. Responses in the presence of the nitric oxide synthase inhibitor N_ω-nitro-L-arginine (L-NOArg) were measured and calculated as a proportion of the control value. Experimental results are expressed as mean(s.e.m.). Numbers are expressed as $x(y)$ where x is the number of strips and y the number of guinea-pigs. Two or three parallel strips were obtained from each guinea-pig IAS. Where appropriate, statistical differences between control and experimental responses were assessed with Student's paired t test. $P < 0·05$ was considered significant.

Results

Injection site

Peroxidase activity at the injection site of experimental animals was confined to the IAS, confirming accurate localization of the injected tracer. In IAS diametrically opposite to the injection site, and in control animals, peroxidase activity was minimal or absent (*Fig. 2*).

Neuronal labelling

In all animals injected with WGA–HRP, peroxidase activity was identified in cells within rectal whole-mount preparations cranial to the sphincter injection site. These cells showed the morphology of neuronal cell bodies with, for the most part, sparse dendritic filling (*Fig. 3*). Axons, where identified, projected in a caudal direction. In control animals no such labelling was found. Erythrocytes, which contain endogenous peroxidase, were present in all preparations but were readily identified by their typical size, shape and linear arrangement in blood vessels.

Co-localization of reduced nicotinamide adenine dinucleotide phosphate diaphorase and horseradish peroxidase activity

NADPH diaphorase enzyme histochemistry revealed the architecture of the myenteric plexus with major and minor interconnecting strands, and identified a subpopulation of enteric neurones within myenteric ganglia (*Fig. 4*). Careful orientation of the whole mounts from injected animals and analysis of photographed areas of interest demonstrated that all labelled neurones (HRP positive) subsequently showed positive staining with NADPH diaphorase. The blue–purple formazan reaction product from the diaphorase reaction was intense but co-localization with peroxidase activity was clear from the position and morphology of labelled neurones in sequential images (*Fig. 5*).

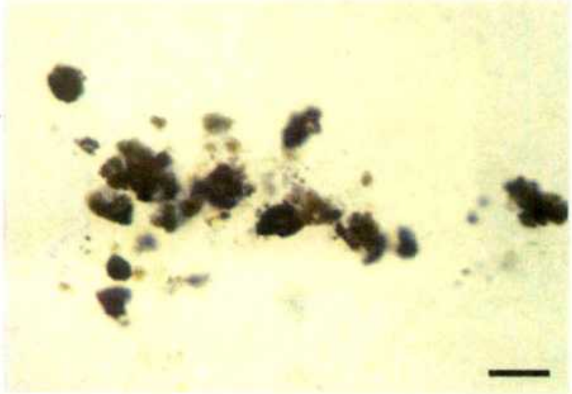

Fig. 3 Peroxidase activity was identified in neuronal cell bodies in whole-mount preparations of the rectal myenteric plexus cranial to the injection site. (Tetramethylbenzidine; bar represents 50 μm)

Rectoanal inhibitory reflex

Anal canal manometry confirmed the presence of a high-pressure zone occupying the distal 2–3 mm of the gut tube. Mean maximal resting pressure was 16 (range 8–20) cmH$_2$O and mean resting rectal pressure 4 (range 2–5) cmH$_2$O. In four animals the anal canal pressure was stable, but in two the anal canal showed regular 'spikes' of pressure at a frequency of 4–5 per min (*Fig. 6*). The rectoanal inhibitory reflex was present in all animals, rectal distension consistently producing profound, immediate reductions in anal canal pressure (*Fig. 7*).

Response of isolated internal anal sphincter to intrinsic nerve stimulation

Strips of IAS developed sustained spontaneous tone at a mean(s.e.m.) basal level of 0·18(0·03) g per mg tissue with superimposed phasic contractions to a level of 0·26(0·02) g

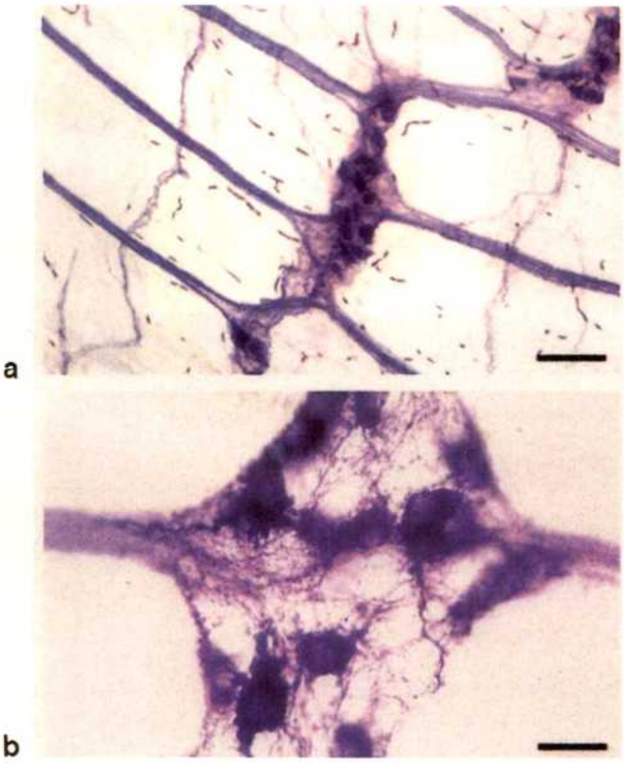

Fig. 4 Reduced nicotinamide adenine dinucleotide phosphate diaphorase histochemistry of whole-mount preparation of rectum from control animal reveals detail of **a** myenteric plexus (bar represents 300 μm) and **b** myenteric ganglion (bar represents 50 μm)

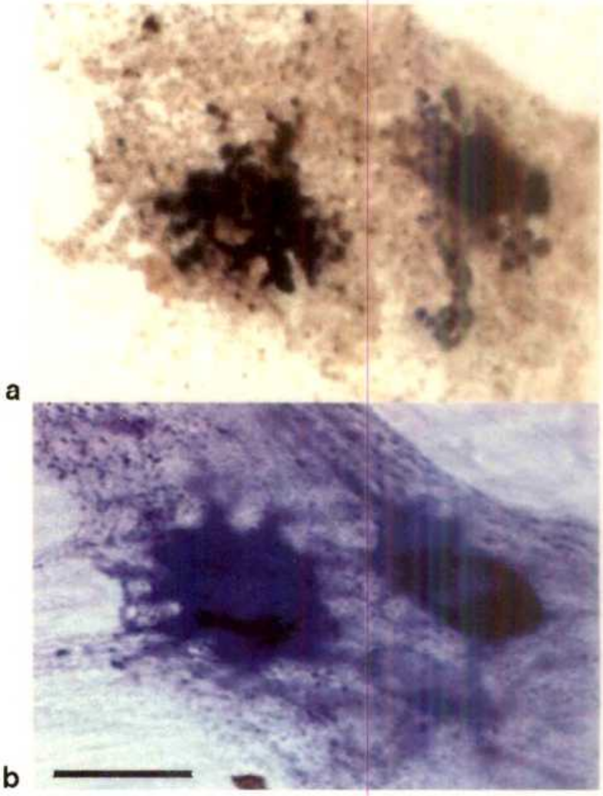

Fig. 5 Sequential images of the same two neurones showing co-localization of peroxidase activity and reduced nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase staining. **a** Tetramethylbenzidine; **b** NADPH diaphorase (bar represents 50 μm)

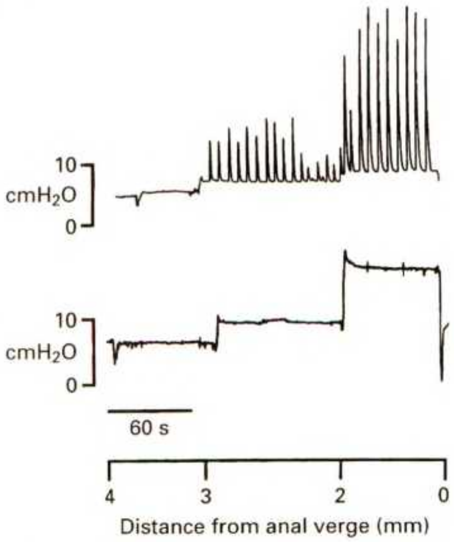

Fig. 6 Anal manometry traces from two animals showing representative anal canal pressures

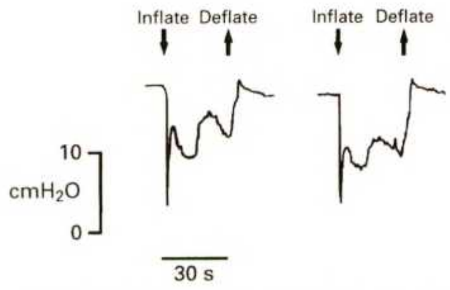

Fig. 7 Rectal distension induces prompt relaxation of the anal canal, representing a positive rectoanal inhibitory reflex

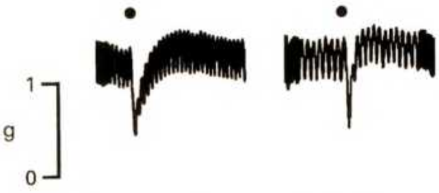

Fig. 8 Electrical field stimulation (●) at 50 V, 0·05 ms, 4 Hz for 1 s elicited neurogenic relaxation of strips of guinea-pig internal anal sphincter *in vitro*

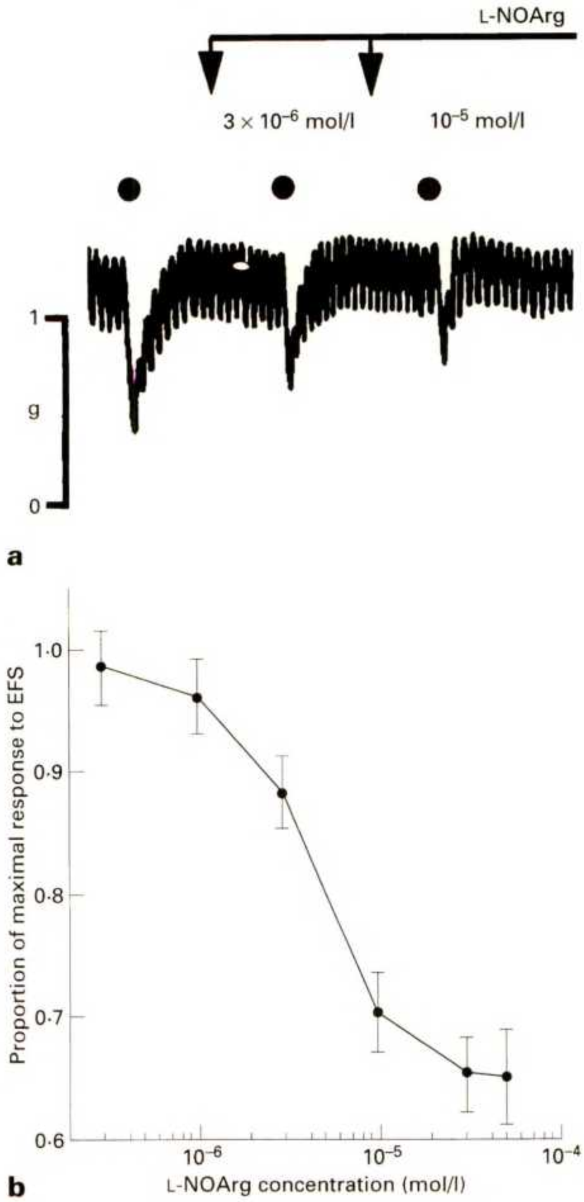

Fig. 9 **a** Response of a single strip of internal anal sphincter to electrical field stimulation (EFS) (●) in the presence of N_ω-nitro-L-arginine (L-NOArg). **b** Dose–response curve showing that the relaxant response was maximally reduced with 3×10^{-5} mol/l L-NOArg. Values represent the mean(s.e.m.) response as a proportion of the control response for each strip ($n = 18(8)$)

per mg tissue. Electrical field stimulation, at a frequency of 4 Hz, elicited maximal relaxation to 52·3(5·4) per cent of mean basal tone (*Fig. 8*). Addition of tetrodotoxin (3×10^{-6} mol/l), a universal nerve toxin, had no effect on the spontaneous activity of the strips but abolished the relaxant response to electrical field stimulation. The presence of atropine and guanethidine in the bathing solution confirmed that responses were mediated by non-adrenergic non-cholinergic nerves. Addition of L-NOArg reduced the response to electrical stimulation in a dose-dependent fashion ($n = 18(8)$; *Fig. 9*). The relaxant response was maximally reduced by 35·2(3·8) per cent ($P < 0·001$) at an L-NOArg concentration of 3×10^{-5} mol/l.

Discussion

Neuronal tracing studies have been performed using a wide variety of neuroanatomical probes including enzymes (e.g. HRP), fluorescent markers, bacterial toxins and plant lectins[10–13]. WGA is the most thoroughly characterized and widely used lectin for retrograde labelling, and WGA–HRP conjugates are superior in sensitivity to free HRP[10,14] as the lectin component binds with oligosaccharides on the cell surface of neuronal membranes inducing absorptive endocytosis and thus enhanced internalization of the probe. The majority of studies tracing neural pathways in the lower gastrointestinal tract have used tracers in animal models to examine projections to and from autonomic ganglia, concentrating on establishing the extrinsic innervation[15–17]. Studies of the projections of intrinsic neurones have relied on lesioning experiments[18] or complex *in vitro* techniques for neurone labelling[19].

The neuronal tracing studies described here demonstrate the presence of an intrinsic rectoanal neuronal pathway with its cell bodies in the myenteric ganglia of the distal rectum and axon terminals in the smooth muscle of the IAS. NADPH diaphorase provides a reliable histochemical marker for neuronal nitric oxide synthase[7,20,21], and consistent co-localization of peroxidase activity and NADPH diaphorase reaction product indicates that the tracer-labelled neurones contain nitric oxide synthase, the enzyme responsible for the production of nitric oxide. This provides direct anatomical evidence that the pathway is nitrergic.

Criticism has been levelled at tracer techniques because of the potential for false-positive labelling due to non-specific uptake via connective tissue and vascular routes[22] or to uptake by axons passing through, but not innervating, the area of interest. The discrete labelling of neurones seen in this study attests to the validity and specificity of the technique in this model. In addition, the enhanced sensitivity of WGA–HRP means that it is an effective tracer at low concentration in small volumes, allowing carefully targeted injection, and evidence suggests that WGA–HRP is not taken up by undamaged axons of passage[23,24].

In vivo recording of guinea-pig anal canal pressures showed that the anatomical IAS has functional importance by generating tone and establishing a negative rectoanal pressure gradient. The presence of a rectoanal inhibitory reflex was confirmed as submaximal distension of the rectum induced prompt anal canal relaxation. The 7-mm balloon is slightly larger than the normal size of guinea-pig faecal pellets (4–6 mm diameter). The technique used to measure anal canal pressures appeared valid as the microtransducer caused minimal distension of the anal canal, was readily used with the station pull-through technique which allowed readings to stabilize at each recording point, and the pressures recorded seemed entirely reasonable. It is well recognized that the recorded value of anal canal pressures is dependent on the technique used and that, in any particular study, it is most important that the method be consistent.

Organ bath pharmacology demonstrated that strips of guinea-pig IAS developed spontaneous myogenic tone (tetrodotoxin resistant) and relaxed in response to electrical field stimulation of the intrinsic nerves. This inhibitory non-adrenergic non-cholinergic response was significantly reduced by the addition of L-NOArg. The stimulus parameters used provoked neurogenic responses (tetrodotoxin sensitive) and avoided direct muscle stimulation. These results provide evidence for the involvement of nitric oxide in inhibitory non-adrenergic non-cholinergic neurotransmission to guinea-pig IAS and are consistent with findings elsewhere in guinea-pig intestine[25,26]. The failure of L-NOArg to abolish the relaxant response completely supports the hypothesis that additional neurotransmitters, such as adenosine 5'-triphosphate or vasoactive intestinal peptide, may be involved.

These studies provide direct anatomical evidence of a descending nitrergic rectoanal neuronal pathway in a guinea-pig model. *In vivo* anal manometry and *in vitro* organ bath studies provide additional evidence that this pathway is responsible for the inhibitory motor innervation of the rectoanal inhibitory reflex.

Acknowledgements

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Case report

Incidental appendicectomy for the long mobile appendix

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The ‘retrospectoscope’ is a valuable instrument available to all surgeons. In this case incidental appendicectomy would have been more rewarding.

Case report

An 80-year-old man underwent stapled anterior resection for rectal carcinoma at 10 cm. Histological examination confirmed a Dukes B tumour. Ten days later he developed small bowel obstruction which did not settle. At a second laparotomy the tip of the long mobile appendix was firmly adherent to the anastomosis, trapping the distal ileum. There was no clinical evidence of an anastomotic leak. Histological analysis showed reactive changes confined to the serosa. The patient died suddenly 6 days later: post-mortem examination identified a large pulmonary embolus.

Discussion

Opinion varies over the appropriateness of incidental appendicectomy[1–3]. If the operation is technically easy, it obviously eliminates a potential site of disease and probably decreases healthcare costs[1]. In ‘clean’ procedures such as open cholecystectomy and gynaecological surgery, however, the merits of appendicectomy are debatable even when augmented with antibiotic prophylaxis[1]. Nevertheless, it is generally agreed that these aged 10–30 years can safely undergo incidental appendicectomy and that those aged 30–50 years should be managed at the surgeon’s discretion[1,2,4]. In the elderly, incidence of acute appendicitis is decreased, and although appendicectomy may be beneficial in terms of avoiding future diagnostic dilemma, it may be associated with increased perioperative morbidity[1,4].

In retrospect, the authors believe that incidental appendicectomy should be considered in all patients undergoing lower gastrointestinal operations, irrespective of age, if the appendix is noted to be long and mobile.

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Short note

Combination of skin temperature and a single white cell count does not improve diagnostic accuracy in acute appendicitis

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Numerous tests, including right iliac fossa (RIF) skin thermography and serial white cell count estimation[1-3], have been suggested to enhance diagnostic accuracy in acute appendicitis. Negative laparotomy rates remain approximately 15–20 per cent[4]. A prospective study was conducted to determine whether abnormalities in RIF or left iliac fossa (LIF) skin temperatures, either alone or in combination with a single white cell count, increase the diagnostic accuracy in acute appendicitis.

Patients and methods

A total of 118 consecutive patients of median age 24 (range 11–82) years who presented with RIF pain were studied. The abdominal skin temperature was measured over McBurney's point and a corresponding point in the LIF by applying a Feverscan (Robinson Healthcare, Chesterfield, UK) for 15 s. This device measures skin temperature to the nearest 0·5°C. Patients were divided into three groups: those with normal skin temperature, those with abnormal skin temperature (RIF temperature greater than that of the LIF, LIF temperature greater than that of the RIF, or RIF and LIF temperatures equally increased); or, specifically, those with RIF temperature greater than that of the LIF. The white cell count of each patient was noted as less than 10×10^9/litre, greater than 10×10^9/litre, or greater than 13×10^9/litre. Final diagnosis was recorded at operation from histological findings or after further investigation.

Results

Some 79 patients had a laparotomy; 63 had proven appendicitis, four mesenteric adenitis, two terminal ileitis, one each of carcinoma of the caecum, ectopic pregnancy and diverticular abscess. There were seven normal laparotomies. Non-surgical diagnoses included seven patients with non-specific abdominal pain, eight with gastroenteritis and 24 had other conditions. Only four patients (6 per cent) with appendicitis had a white cell count greater than 13×10^9/litre and a RIF temperature greater than the LIF temperature (*Table 1*). This rose to 23 (37 per cent) with a white cell count greater than 10×10^9/litre and any abnormal skin temperature. In patients with appendicitis, 30 (48 per cent) demonstrated either an increased RIF temperature or a count greater than 13×10^9/litre, rising to 52 (83 per cent) when the count was greater than 10×10^9/litre or there was any skin temperature abnormality. The sensitivity of raised RIF temperature in acute appendicitis was 80 per cent but the specificity was low (25 per cent). These values did not improve significantly when applied to the various combinations described earlier.

Table 1 Patients presenting with abnormal skin temperature and increased white cell count

	All patients ($n = 118$)	Patients with confirmed appendicitis ($n = 63$)
Abnormal temperature	57 (48)	34 (54)
RIF > LIF temperature	20 (17)	16 (25)
WCC > 10×10^9/litre	50 (42)	39 (62)
WCC > 13×10^9/litre	25 (21)	19 (30)

Values in parentheses are percentages. RIF, right iliac fossa; LIF, left iliac fossa; WCC, white cell count

Discussion

This study shows that the routine measurement of iliac fossa temperature is of limited benefit in the diagnosis of acute appendicitis. Sensitivity is reasonable and similar to that of a single white cell count alone, but specificity is poor and fails to improve when abdominal skin temperature is measured in combination with the white cell count. If the inflammatory process in the appendix raises the local skin temperature, then presumably the poor predictive value of this test is caused by the varying stage of the disease at presentation and the anatomical position of the appendix. Until a more efficient method of assessing the temperature can be found, the decision to operate must continue to be based on clinical findings.

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Screening for colorectal cancer with an immunological faecal occult blood test: 2-year follow-up

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This study is a 2-year follow-up of an average-risk population offered screening with both Haemoccult and Hemeselect tests to determine the interval cancer rate, and thus sensitivity. The effect on compliance with Hemeselect of testing over 1 day rather than 3 days was investigated in a separate cohort. In the first study, 3948 subjects received tests; 1489 (37·7 per cent) completed both tests and 148 had a positive result, 17 (1·1 per cent) were Haemoccult positive and 145 (9·7 per cent) were Hemeselect positive. Investigation of 142 patients revealed ten with cancer (Dukes stage A, seven; B, one; C, two). All were detected by Hemeselect but only one was Haemoccult positive. After a median follow-up of 35 (range 26–43) months, seven further patients developed colorectal cancer (stage A, one; B, three; C, three) but none followed a negative Hemeselect test (100 per cent sensitivity). In the second study 2703 subjects were offered Hemeselect tests. Compliance for testing over 1 day (48·6 per cent) was significantly better than that over 3 days (43·1 per cent) ($\chi^2=8\cdot1$, 1 d.f., $P<0\cdot01$). Hemeselect is a promising screening test for the early detection of colorectal cancer.

To be effective, cancer screening programmes require a test that is sensitive but acceptable to the population. The guaiac-based Haemoccult (SmithKline Diagnostics, San Jose, California, USA) faecal occult blood (FOB) test may not be sufficiently sensitive in population screening for colorectal carcinoma. Hemeselect (SmithKline Diagnostics), an immunological FOB test, is more sensitive for symptomatic colorectal cancer[1,2] but its sensitivity in the setting of population screening is unknown. A 2-year follow-up of an average-risk population offered screening Hemeselect tests[3] is presented here to determine the interval cancer rate and, thus, sensitivity. The effect on compliance with Hemeselect of testing over 1 day rather than 3 days was investigated in a separate cohort.

Patients and methods

A total of 4018 asymptomatic subjects aged 50–75 years were offered screening with both Haemoccult and Hemeselect tests. The method of invitation, testing and investigation of subjects returning positive tests has been described previously[3]. Subjects have been followed for the development of colorectal neoplasia by information received from general practitioners and by monitoring the histopathology records of local hospitals. Screened practices refer patients only to the hospitals that are included in the study. The same histopathology laboratories report specimens from the local private hospitals. Follow-up from screening was a median of 35 (range 26–43) months.

The positive rate of Hemeselect tests read, according to manufacturer's instructions, over 3 days at 1:8 dilution may be too high for screening an average-risk population[5]. The positive rate can be reduced by increasing the dilution at which the Hemeselect test is read and/or by reducing the number of days of testing[4]. The latter might increase test compliance. A second study was designed to compare the compliance of 1-day testing (read at 1:8 dilution) with 3-day testing (read at 1:32 dilution). Subjects were randomized to receive only Hemeselect tests to be completed over either 1 or 3 days. The method was otherwise unchanged.

Results

In the first study 1489 (37·7 per cent) of 3948 subjects who received tests completed both, and 148 had a positive result (17 (1·1 per cent) were Haemoccult positive and 145 (9·7 per cent) were Hemeselect positive). Investigation of 142 patients revealed ten with cancer (Dukes stage A, seven; B, one; C, two). All were detected by Hemeselect (positive predictive value (PPV) 6·9 per cent) but only one was Haemoccult positive (PPV 5·9 per cent). During follow-up, seven patients developed colorectal cancer (stage A, one; B, three; C, three). Six presented symptomatically in patients between 10 and 17 months after refusal of the offer of FOB testing and one was diagnosed during follow-up for adenoma. No patient has presented with cancer in the interval following a negative Hemeselect test result.

In the second study 2703 subjects were offered Hemeselect tests. Compliance, positive test rate and yield for 1- and 3-day testing are shown in *Table 1*. Compliance for testing over 1 day (48·6 per cent) was significantly better than that over 3 days (43·1 per cent) ($\chi^2=8\cdot1$, 1 d.f., $P<0\cdot01$).

Table 1 Hemeselect testing over 1 *versus* 3 days

	Test period	
	1 day	3 days
Invited	1353	1350
Post office returns*	16	12
Accepted (compliance)	650 (48·6)	577 (43·1)†
Returned positive tests (positive rate)	26 (4·0)	35 (6·1)
Investigated	24	29
Cancers detected	0	2

Values in parentheses are percentages. *Refers to any invitation to screening that is returned to the post office marked 'dead' or 'gone away'. †$P<0\cdot01$ (1 *versus* 3 days, χ^2 test)

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Discussion

Three studies[3–6] have assessed the performance of Hemeselect against other FOB tests in screening average-risk individuals. From a total of 11 208 subjects screened, the positive rate for Hemeselect has been 4·9–11·2 per cent[3–6], but 6·5 per cent if only the first day's card was read[5]. Thirty-two patients with cancer were detected, of whom 30 returned positive Hemeselect tests[3–6]. However, none of these reports included follow-up to determine the number of patients returning negative Hemeselect tests who subsequently developed cancer ('interval cancers'). A 2-year follow-up of the present screening study cohort[3] found no interval cancers. Although the positive test rate is high, the PPV for carcinoma of 3·4–6·9 per cent and sensitivity as high as 100 per cent suggests that Hemeselect should be evaluated further. The increase in compliance with 1-day testing was small and may be offset by a reduced yield.

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Physiological and clinical outcome of anterior sphincteroplasty

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A total of 55 women underwent sphincteroplasty for the treatment of faecal incontinence related to anterior defects. Patients were followed prospectively for a mean of 29 months to evaluate the outcome overall and according to age. All patients were evaluated clinically by means of a questionnaire and graded using an incontinence scoring system ranging from 0 (perfect continence) to 20 (complete incontinence). Some 52 patients (95 per cent) had had a previous vaginal delivery and 30 (55 per cent) had a history of previous anal sphincter repair. Physiological and functional parameters in patients with a successful outcome ($n = 39$) were compared with those in patients with a poor outcome ($n = 16$). The results were also compared in patients under ($n = 39$) and over ($n = 16$) 60 years of age. Overall, patients with a successful outcome had a significant change in mean and maximal resting and squeeze pressures. These changes correlated well with the increase in the high-pressure zone (HPZ) length from 1·0–2·2 cm ($P = 0{\cdot}0002$) and with functional outcome (change in incontinence score from 15·3 to 5·8; $P < 0{\cdot}0001$). In patients over 60 years of age, a significant change in mean squeeze pressure ($P = 0{\cdot}03$) and HPZ length ($P = 0{\cdot}01$) was noted and correlated with functional outcome (change in incontinence score from 14·3 to 6·4; $P < 0{\cdot}0001$). A successful outcome after anterior sphincteroplasty is related to improvement in sphincter function even in an older population. These results demonstrate that age itself does not seem to be a predictor of poor outcome. Patients should not be denied a repair exclusively on grounds of age.

The exact incidence of faecal incontinence is unknown. Nevertheless, it is a very common condition, especially in women, due to obstetric injury. In older women with a previous obstetric history, the effects of age may contribute to faecal incontinence, as physiological changes occur naturally. Such changes have led to a fear of poor outcome after sphincter reconstruction in these patients. The aims of the present study were first to evaluate clinically and physiologically the results of anterior sphincteroplasty in a large group of women compared with previous series[1] and second to determine the effect of age on these results.

Patients and methods

Patients

All patients who underwent anterior sphincteroplasty for anterior defects between September 1989 and July 1994 were evaluated (*Table 1*). Patient complaints included incontinence of solid, liquid and gas (*Table 2*). Sixteen of the 55 patients were over 60 years of age. The most common aetiology overall was obstetric injury (84 per cent) followed by surgical procedure (15 per cent) and trauma (2 per cent). In all patients aged over 60 years the aetiology was previous obstetric history. Clinical and functional follow-up was obtained in all patients at a mean of 29 (range 3–61) months. Patients were evaluated clinically to exclude any other anorectal conditions. The type and grade of incontinence were assessed using an incontinence scoring system that was included as part of an incontinence questionnaire completed by the patients before and 3–6 months after the surgical procedure. This incontinence scoring system included information about the necessity of wearing a pad and lifestyle alteration due to incontinence (*Table 3*). Functional outcome was then obtained based on the scoring system, on patients' subjective analysis of outcome (excellent, good, fair or poor) and by clinical evaluation. Subsequently, patients were divided into a success or failure group and, ultimately, the results of patients under and over 60 years of age were compared. Outcome was considered

Table 1 Patient demographics

Age (years)	48 (27–72)
Duration of incontinence (years)	7·4 (1–24)
No. of vaginal deliveries	2·1 (1–6)
No. of episiotomies	2·2 (0–4)
No. of previous primary repairs	2·2 (0–4)
No. of previous secondary repairs	0·8 (0–4)
Follow-up (months)	29 (3–61)

Values are mean (range) for 55 patients

Table 2 Frequency of incontinence in 55 patients

	Gas	Liquid	Solid
≥ 1 per day	41	31	24
< 1 per day, ≥ 1 per week	12	13	16
< 1 per week, ≥ 1 per month	2	7	11
< 1 per month	0	4	4
Never	0	0	0

Table 3 Continence grading scale

	Frequency				
Type of incontinence	Never	Rarely*	Sometimes†	Usually‡	Always§
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Requires pad	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4

The score ranged from 0 (perfect continence) to 20 (complete incontinence). *Less than once per month; †less than once per week, once or more per month; ‡less than once per day, once or more per week; §more than once per day

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successful when the patient's subjective response to the questionnaire was 'excellent' or 'good', and poor when other subjective responses were obtained

Anal physiology

Physiological evaluation included anal manometry, measurement of pudendal nerve terminal motor latency (PNTML) and electromyography (EMG). Manometry was performed before and after operation using a water-perfused catheter technique described previously[2,3]. The mean and maximal resting and squeeze pressures, length of the high-pressure zone (HPZ), rectal sensation and rectal capacity were analysed. EMG and PNTML studies were performed with a Nicolet Viking II (Madison, Wisconsin, USA) EMG apparatus. A bipolar concentric 23-G Teca needle 7·7 mm in length and 0·64 mm in diameter (Teca, Pleasantville, New York, USA) was used for EMG, and a disposable St Mark's stimulating electrode (Dantek, Skovlund, Denmark) was used for measurement of PNTML. Normal PNTML was taken as less than or equal to 2·2 ms. The exact methodology used has been described previously[4,5].

Complete preoperative and postoperative evaluation of the anal sphincter by endoanal ultrasonography was obtained after 1990. Ultrasonography was performed in the lateral decubitus position using a Bruel and Kjaer (Naerum, Denmark) ultrasonographic scanner type 1846, with a rotating endoprobe type 1850, equipped with a 7-MHz transducer[6]. Discontinuity of the sphincter muscles at more than two levels was considered a defect. Additional echoic abnormalities included thinning, scarring and fibrosis.

Surgical procedure

The surgical procedure was performed after the patients had been given parenteral antibiotics and full mechanical bowel preparation. Operation was undertaken in the prone jack-knife position under general anaesthesia. A 120–180° anterolateral curvilinear incision was performed to expose the extrasphincteric plane. The dissection was deepened to mobilize the external and internal anal sphincters. Scar tissue was left in place to provide added support. Multilayer overlapping sphincteroplasty was performed as described previously[1]. The wounds were closed in a Y-fashion, leaving the central portion open for drainage, no stomas were used. The procedure has been reported in greater detail previously[7,8].

Statistical analysis

All data were correlated and analysed statistically with a commercially available statistical program (Instat Graphpad Software, San Diego, California, USA, 1993). Manometric data and incontinence scores were compared with Student's t test. Ultrasonographic and pudendal nerve studies were evaluated by Fisher's exact test. Significance was assigned to any P value of less than 0·05.

Results

Clinical and functional outcome

Overall, the success rate of sphincteroplasty was 71 per cent. Thirty-nine patients rated the results as either excellent ($n = 13$) or good ($n = 26$), and 16 considered the outcome to be fair ($n = 5$) or poor ($n = 11$). A good correlation was obtained between patient outcome and clinical and physiological evaluation after surgery. A significant change in the frequency and type of incontinence was observed in patients who had a successful repair (*Table 4*). Conversely, such improvement was not seen in patients in whom the repair had failed. There were no differences in the functional results for patients under and over 60 years of age, for whom success rates were 69 and 75 per cent respectively (*Table 5*). Minor complications occurred in only three patients (5 per cent) and consisted of bleeding during the night following the procedure, faecal impaction and a chronic perineal sinus; all were treated conservatively. No infectious complication occurred.

Pathophysiological results

Manometric data in patients with a successful outcome showed an increase in mean and maximal resting pressures, and in mean and maximal squeeze pressures, as well as an increase in the length of the HPZ (*Table 6*). In patients aged over 60 years a significant change was observed in squeeze pressures and length of the HPZ (*Table 5*).

Table 4 Postoperative frequency of incontinence related to success ($n = 39$) or failure ($n = 16$) of the repair

	Gas		Liquid		Solid	
	Success	Failure	Success	Failure	Success	Failure
≥ 1 per day	11	12	1	9	0	7
< 1 per day, ≥ 1 per week	3	2	3	3	2	5
< 1 per week, ≥ 1 per month	8	1	4	0	6	2
< 1 per month	11	1	15	3	17	2
Never	6	0	16	1	14	0

Table 5 Physiological and functional results related to age

	Age 27–60 years ($n = 39$)*			Age 61–72 years ($n = 16$)†		
	Preoperative	Postoperative	P‡	Preoperative	Postoperative	P‡
Mean incontinence score	14·9	9·3	0·0001	14·3	6·4	0·0001
Mean resting pressure (mmHg)	29	36	0·03	33	41	n.s.
Mean maximal resting pressure (mmHg)	51	51	n.s.	53	57	n.s
Mean squeeze pressure (mmHg)	24	41	0·0001	23	33	0·03
Mean maximal squeeze pressure (mmHg)	50	66	0·003	44	61	0·04
High-pressure zone (cm)	1·4	2·2	0·05	1	2·2	0·01

Success rates were *69 and †75 per cent. n.s., Not significant ‡Student's t test.

Table 6 Physiological and functional results ($n = 55$)

	Successful procedure ($n = 39$)			Failed procedure ($n = 16$)		
	Preoperative	Postoperative	P*	Preoperative	Postoperative	P*
Mean incontinence score	15·3	5·8	0·0001	14·2	13·1	n.s.
Mean resting pressure (mmHg)	25	39	0·0002	36	33	n.s.
Mean maximal resting pressure (mmHg)	48	61	0·04	53	46	n.s.
Mean squeeze pressure (mmHg)	22	45	0·0001	21	22	n.s.
Mean maximal squeeze pressure (mmHg)	46	70	0·0001	42	39	n.s.
High-pressure zone (cm)	1·0	2·2	0·0002	1·6	1·8	n.s.
PNTML (n)						
Normal	29	—	—	11	—	—
> 2·3 ms	3†	—	—	5	—	—
Endoanal ultrasonography						
Normal (n)	—	17	—	—	3	—
Abnormal (n)	—	2‡	—	—	10	—

PNTML, pudendal nerve terminal motor latency; n.s., not significant. *Student's t test; †$P = 0·09$, ‡$P < 0·0001$ *versus* patients whose procedure failed (Fisher's exact test)

Table 7 Results of published series

Reference	Year	n	Mean (range) age (years)	Women (%)	Obstetric cause (%)	Colostomy (%)	Physiological evaluation	Good or excellent result (%)
Fang *et al.*[29]	1984	79	(17–68)	78	88	0	No	89
Laurberg *et al.*[15]	1988	19	(23–64)	100	100	—	Yes	47
Yoshioka and Keighley[30]	1989	27	34 (17–81)	52	70	37	Yes	74
Fleshman *et al.*[12]	1991	28	38 (22–75)	100	100	0	Yes	75
Engel *et al.*[16]	1994	55	32 (26–52)	100	100	24	Yes	76
Engel *et al.*[31]	1994	28	41 (22–66)	89	53	36	Yes	75
Simmang *et al.*[28]	1994	14	66 (51–81)	100	79	0	Yes	93
Present study	1996	55	48 (27–72)	100	84	0	Yes	71

Neurological assessment of the anal sphincter showed EMG abnormalities in the majority of patients ($n = 38$) and a good correlation was obtained between EMG, ultrasonographic and surgical findings. The most common EMG findings were polyphasia and decreased motor unit potentials. Overall, mean PNTML was 2·0 ms; it was abnormal in five of 16 patients in whom the operation failed and in three of the 39 who had a successful procedure ($P = 0·09$).

Endoanal ultrasonography was performed after operation in 32 patients. Of 39 patients who had a good outcome, 19 underwent postoperative ultrasonography; 17 had normal anal anatomy after sphincter repair and two presented with some thinning of the external anal sphincter or scarring. Of the 16 patients in whom the repair failed, 13 underwent endoanal ultrasonography, and ten of these had a persistent echoic abnormality (*Table 6*). Two patients had a normal overlap and one had scarring at one level of the anal canal.

Discussion

In the evaluation of patients with faecal incontinence it is important to establish the exact aetiology and to assess clinically the type and degree of incontinence as well as its effect on the patient's lifestyle[9–11]. All patients in the present study were assessed before and after surgery using the scoring system shown in *Table 3*[11]. In addition to subjective classification, objective assessment is important to assist in assignment and follow-up of therapy[12]. Anal manometry helps to document postoperative change in anal pressure and in the length of the HPZ[1]. In this study, a good correlation was seen between patients with a successful outcome and an improvement in anal pressures. Persistently low anal pressure in patients with a poor outcome indicates the need for alternative treatment such as biofeedback[13] or, when feasible, a different surgical approach[14].

The importance of neurological assessment of the pudendal nerves before surgery has been described previously[2,4,15]. In fact, only one series has failed to demonstrate a correlation between pudendal neuropathy and poor outcome[1,16,17]. Because of the small number of patients in the present series this correlation was not statistically significant. Nevertheless, five of the 16 patients with a poor outcome had pudendal neuropathy.

In one patient, postoperative faecal impaction led to partial disruption of the repair and consequent poor outcome. Diabetic neuropathy contributed to the poor outcome in another patient[18]. The remaining two patients in whom the procedure failed had a history of severe damage to the perineal body by multiple fistulotomies, and restoration of the anatomy was difficult to achieve. One of these two patients underwent a stimulated gracilis transposition[19] with a successful outcome. Tjandra and colleagues[20] compared EMG and endoanal ultrasonography for the evaluation of faecal incontinence and concluded that the latter was more sensitive, less painful, easier to perform and as accurate as EMG in the preoperative and postoperative assessment of the anal sphincters[20]. In the present series, persistent echoic abnormalities in anal sphincter architecture seen by endoanal ultrasonography proved to be an important factor related to poor outcome. Ten of the 13 patients in whom the repair failed and who underwent ultrasonography after surgery presented with echoic abnormalities. However, in these patients a second sphincter repair may be possible[21,22].

Faecal incontinence in the elderly has been treated more conservatively because of the fear of poor outcome. McHugh and Diamant[23] compared 143 incontinent patients with a control group of 157 healthy subjects. They showed that the process of ageing significantly influences resting pressures, with women showing a much greater age-related effect than men. Ageing also affects mean squeeze pressure and pudendal latency, although to a lesser extent[24–27]. In the present series a significant postoperative increase in squeeze pressure and in the HPZ length in patients over 60 years was demonstrated; these objective changes correlated well with a significant improvement in sphincter function. Thus age itself is not a predictor of poor outcome after sphincter repair. Furthermore, it was demonstrated that careful patient selection for the repair is essential to exclude neuropathy and to demonstrate a clear anterior defect, either by clinical examination, EMG, endoanal ultrasonography or ideally by a combination of the three methods.

This series is the largest in which an older group of patients has been evaluated for more than 2 years after surgery. Simmang *et al.*[28] reported a series of 14 incontinent patients with a mean age of 66 years who underwent sphincteroplasty with similar functional and physiological results. The present authors observed that older women sustained longer periods of faecal incontinence before seeking medical treatment.

In conclusion, anterior multilayer overlapping sphincteroplasty is a good procedure for the treatment of faecal incontinence secondary to anterior sphincter defects (*Table 7*). This operation has the advantages of a low incidence of perineal infection and it restores normal anatomy and function. Physiological investigation is an important tool in the evaluation of incontinent patients and can be used to predict outcome. It was demonstrated that age itself does not seem to be a predictor of poor outcome; all women at least 72 years of age in whom an anterior external anal sphincter defect is present can safely undergo multilayer overlapping sphincteroplasty. However, neuropathy augurs a poor outcome.

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Case report

Carcinoma in an ileoanal pouch after restorative proctocolectomy for familial adenomatous polyposis

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The first case is described of a patient who developed adenocarcinoma in an ileoanal pouch after restorative proctocolectomy for familial adenomatous polyposis (FAP).

Case report

A 28-year-old man with FAP underwent restorative proctocolectomy with anal mucosectomy in 1991. Histological examination confirmed numerous adenomatous polyps with no evidence of malignancy. Three years later he presented with lower abdominal pain, frequent loose bloody bowel actions, weight loss and anaemia. Pouchogram (*Fig. 1*) showed a large polypoid tumour. A biopsy specimen revealed adenocarcinoma. Abdominoperineal excision of the pouch and anal canal was performed. Histological examination confirmed infiltrating adenocarcinoma of small bowel origin with nodal metastasis.

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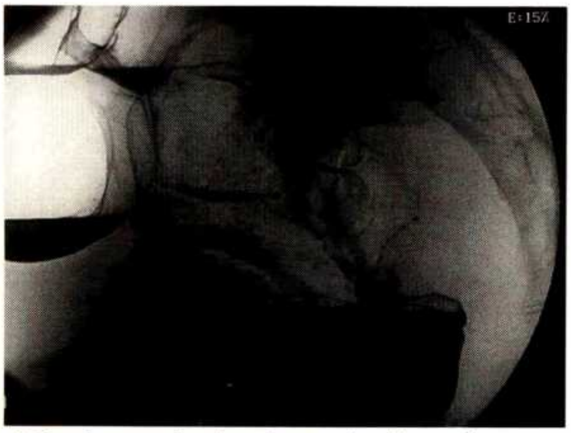

Fig. 1 Pouchogram showing a large polypoid posterior carcinoma with wide presacral space

Discussion

Three previous cases have been reported of carcinoma arising in an ileoanal pouch after restorative proctocolectomy for ulcerative colitis[1]. In FAP it is now well recognized that adenomas may be found in the stomach, duodenum and small intestine as well as in the colon. The malignant potential of non-colonic adenomas is low with the exception of periampullary adenomas[2].

Adenocarcinoma in an ileostomy is a rare but well documented complication, which tends to occur many years after stoma formation. A total of 18 patients have been reported, four occurring in those with FAP[3]. Adenocarcinoma may develop in small bowel mucosa that has undergone metaplasia to resemble colonic epithelium with subsequent adenoma formation[2]. The malignant potential of the small bowel may also be increased by subtotal villous atrophy, increased cell turnover and shortening of the villi coupled with bacterial proliferation and bile salt pooling[4]. More recently, adenocarcinoma has been reported as developing in an ileoanal anastomosis in a patient with FAP[5].

It has been suggested that conservative proctocolectomy may not be a 'cancer free' alternative to colectomy and ileorectal anastomosis[2]. This risk, although undoubtedly small, has now been shown to be a real one.

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Surgical workshop

Ileocaecostomy: an alternative surgical procedure for antegrade colonic enema

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Intraoperative antegrade colonic lavage via a tube caecostomy is an established method of cleansing the large bowel[1,2]. The use of the appendix as a conduit (appendicostomy) for the introduction of drugs into the colon was first proposed by Keetley[3] in 1895 as a treatment for chronic ulcerative colitis. More recently appendicocaecostomy has been advocated as a surgical procedure for children with faecal incontinence[4] and adults with chronic idiopathic constipation[5]; the stoma provides a continent, intermittently catheterizable conduit for the administration of an antegrade enema. In the absence of an appendix it is suggested that a conduit can be fashioned from tubularized ileum or caecum. However, there is a considerable incidence of stomal stenosis with these procedures, and attempts to fashion a neoappendix from tubularized caecum often fail. An alternative operation, namely ileocaecostomy, is described.

Surgical technique

A right iliac fossa gridiron incision is made and the caecum, appendix and terminal ileum are delivered into the wound. Appendicectomy is performed if the appendix is present. The terminal ileum is divided between clamps 5–7 cm from the ileocaecal valve. A colotomy is made in the ascending colon 7–10 cm distal to the ileocaecal valve, and intestinal continuity is restored by anastomosis between the proximal terminal ileum (B in *Fig. 1*) and the ascending colon (C in *Fig. 1*) using two layers of continuous 2/0 polyglactin. The distal terminal ileum (A in *Fig. 1*) is delivered through a separate stab incision lower in the anterior abdominal wall as the ileocaecostomy, and is intubated with a Foley catheter. An antimesenteric full-thickness V-shaped segment is excised from the stoma before mucocutaneous suture, to give an ileocaecostomy of smaller diameter (*Fig. 2*).

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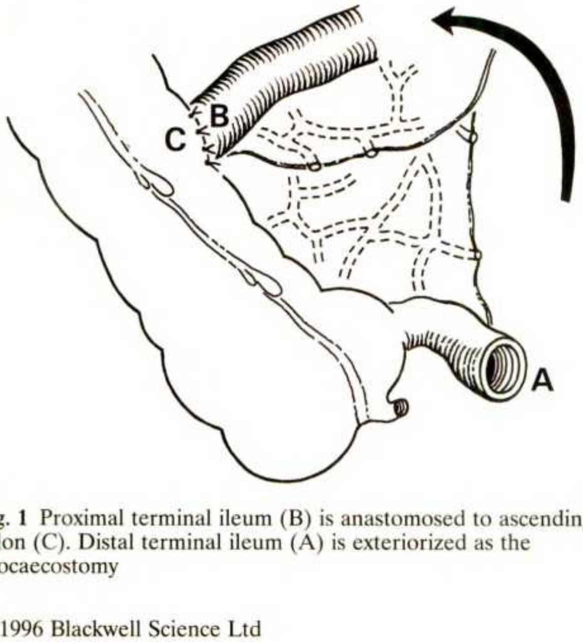

Fig. 1 Proximal terminal ileum (B) is anastomosed to ascending colon (C). Distal terminal ileum (A) is exteriorized as the ileocaecostomy

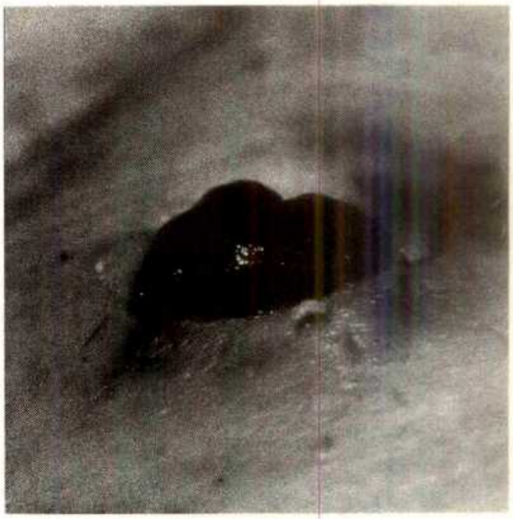

Fig. 2 Appearance of the ileocaecostomy

The stoma remains intubated for 3 weeks, and small volumes of physiological saline are irrigated through the catheter from day 5. This volume is gradually increased until satisfactory emptying of the colon is achieved (up to 2 litres of saline may be necessary). Intermittent irrigation is performed every 48–72 h following removal of the catheter.

This procedure has been carried out in seven patients with chronic idiopathic constipation. Stomal stenosis has not yet occurred in any patient. The ileocaecostomy is fully continent in six patients. One patient, however, experiences significant leakage after irrigation. The stomas are easy to intubate, and all patients report excellent results from antegrade continence enemas. A small pad is worn over the stoma because of mild mucous leakage.

Discussion

Appendicocaecostomy is a simple operation that produces good results in children, is easily reversed and does not interfere with continence mechanisms[4]. Experience of this technique in adults, however, has shown a high incidence of stomal stenosis and uncatheterizable conduits[5]; this is particularly the case after fashioning a neoappendix from tubularized bowel. Incorporation of a skin flap at the mucocutaneous junction has been advocated as a means of decreasing this complication, but stenosis may occur despite this manoeuvre[4].

Ileocaecostomy is proposed as an alternative conduit for administration of antegrade enemas. In the authors' experience there have been no cases of stenosis of the ileocaecostomy and continence of the stoma may be a consequence of the ileocaecal valve placed in the conduit. Nevertheless, the theoretical possibility remains of an incompetent ileocaecal valve allowing excessive leakage; anastomosis of the ileum at a greater distance from the caecum may ameliorate this problem. Little is known about the long-term effects of such procedures, particularly whether the initial improvement experienced by these patients is maintained. Caution is, therefore, required before recommending this apparently simple procedure as a panacea for the treatment of this complex group of patients.

Acknowledgements

Fig. 1 was drawn by Mr Keith Harrison of the Department of Medical Illustration, Withington Hospital, Manchester, UK.

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Case report

Rectal ischaemia following hypovolaemic shock

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Rectal ischaemia is a rare condition, most commonly seen following aortic surgery, in which hypotension develops secondary to blood loss.

Case report

A 24-year-old man was admitted as an emergency following a deep penetrating injury to the right cubital fossa. Damage had been sustained to the brachial artery, median and ulnar nerves, and there had been extensive blood loss before admission. Blood pressure on admission to hospital was unrecordable; the patient sustained a cardiac arrest on arrival, from which he was successfully resuscitated. Thereafter an operation was performed for reconstruction of the brachial artery and repair of the median and ulnar nerves. The estimated duration of hypotension from time of injury was 2 h.

After operation it was apparent the patient had sustained ischaemic damage to the brain and spinal cord, as evidenced by neurological signs. On the eighth postoperative day he developed a high fever and diarrhoea. All blood and stool cultures including *Clostridium difficile* were negative. He was treated with ciprofloxacin and Lomotil (Searle, High Wycombe, UK), and the diarrhoea subsided. On the 12th day the patient passed a small volume of blood per rectum but remained haemodynamically stable. The following day further rectal bleeding occurred, the haemoglobin level dropping by 3 g/dl; the clotting profile was normal. Sigmoidoscopy revealed a rectum full of fresh blood, while upper gastrointestinal endoscopy was normal. Laparotomy was performed in view of the patient's increasing instability and blood loss. The rectum was found to have undergone necrosis with a sealed perforation in the mid-rectum. The rectum was removed at the level of the anorectal junction with the formation of an end stoma. The rest of the colon from the level of sigmoid was viable without any evidence of ischaemia. Histological examination confirmed ischaemic ulceration and perforation of the rectum. The patient recovered from the operation but was in a persistent vegetative state. He died 10 weeks later from a massive pulmonary embolus.

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Discussion

Rectal ischaemia is rare because of the rich blood supply of the organ. Ischaemic colitis may complicate aortic surgery, the most common site being the splenic flexure[1]. Acute rectal ischaemia can also follow aortic surgery[2], accidental embolization of the rectal vasculature and tumour oedema[3]. One case of rectal ischaemia has been reported following anaphylactic shock[4]. As far as the authors are aware, this is the only report of rectal ischaemia occurring as a result of hypovolaemic shock sustained through trauma.

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Use of the carbon dioxide laser to manage cutaneous metastases from malignant melanoma

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Between October 1988 and November 1994, 100 patients with cutaneous metastases from malignant melanoma were treated by carbon dioxide laser ablation under local or general anaesthesia as appropriate. There were minimal postoperative complications and most wounds healed within 6 weeks. A total of 34 of the 53 patients in this series with stage IIIa disease were controlled with four or fewer laser ablations during the first year from presentation. This technique provides a simple effective alternative to hyperthermic isolated limb perfusion with melphalan. Patients with disease not controlled by laser can be considered for isolated limb perfusion.

Malignant melanoma metastasizes in a diverse pattern via lymphatic and haematogenous routes and can spread to the skin and subcutaneous tissues without detectable disease in other organs. Left untreated, cutaneous metastases enlarge and ulcerate, becoming painful and unsightly. The majority of patients with cutaneous manifestations of metastatic melanoma will develop fatal systemic disease but, in the interim, cutaneous and subcutaneous deposits require palliation, preferably by a simple treatment with low attendant morbidity.

Where the number of metastases are few the treatment of choice is local surgical excision, but this is not practicable when deposits are numerous and recur within a short time. Malignant melanoma is relatively resistant to both radiotherapy and systemic chemotherapy[1]. Diathermy and cryoablation have been suggested as possible treatments but have not yet been reported in the literature.

If the lesions are confined to the limb of origin isolated limb perfusion (ILP) is an important treatment option[2–5]. However, ILP is a major operation which requires hospital admission and has a significant associated morbidity rate[4,6]. The results of hyperthermic ILP with melphalan are poor when judged in terms of response rates and duration of response[7,8]. Because of the intrinsic limitations of ILP the use of carbon dioxide laser ablation of cutaneous and superficial subcutaneous deposits of malignant melanoma was investigated. The wavelength of the carbon dioxide laser is 10·6 μm and the beam is readily absorbed by soft tissues so that tumour vaporization is rapid and precise with minimal dissipation of heat. The preliminary results of laser vaporization have been reported previously[9]. The conclusions presented in this paper support the original findings.

Patients and methods

Some 100 patients (median age 69 (range 24–88) years) with cutaneous and superficial subcutaneous metastases of malignant melanoma, which were too numerous or recurring too frequently for conventional surgical excision, were selected for treatment with the carbon dioxide laser. Those who had large fungating lesions (greater than 2 cm in diameter), full-thickness lesions on the eyelid, or deep subcutaneous deposits were considered unsuitable for laser vaporization. Metastases overlying bony prominences were treated by laser provided they were smaller than 2 cm in diameter and not directly invading bone. Patients who had developed recurrent disease after previous ILP were included, as were those in whom ILP was contraindicated due to distant spread. Fifteen patients had undergone at least one ILP after which they had developed recurrent disease before undergoing laser treatment. Forty-one patients whom the authors would previously have considered as suitable for ILP were selected for laser ablation in the knowledge that perfusion would remain an option if laser therapy failed to achieve local control. The patients' primary tumour sites are shown in *Table 1*, and M. D Anderson stage at presentation in *Table 2*. The M. D. Anderson clinical staging system is summarized in *Table 3*

A Sirius 300 portable carbon dioxide laser (Shanning, Swansea, UK) was used. This model has a range of power of 1–30 W. The laser beam is emitted through a 50-mm lens from an articulated arm. At the focal point the beam diameter is 0·05 mm Because the laser's wavelength (10·6 μm) is in the far infrared region of the spectrum, a red helium neon aiming beam is included. The articulated arm allows the laser to be aimed at multiple points sequentially without needing to adjust the patient's position

Treatment was performed under local or general anaesthesia depending on the number and position of lesions. Lignocaine with adrenaline was used for local anaesthesia to minimize bleeding during the procedure. Aqueous chlorhexidine was used for skin preparation and the surgeon wore sterile gloves. The smoke plume produced by tumour vaporization was removed by strong suction, the evacuator tip held in close proximity to the ablation site. This is an important point of technique as, without strong suction, thermal damage to adjacent skin can occur resulting in inflammatory changes and delayed healing. All personnel in the theatre wore protective goggles approved for use with the carbon dioxide laser by the British Standards Institution. Theatre doors were alarmed or locked to prevent inadvertent entry by unprotected staff. The majority of metastases extended through the full skin thickness and consequently a full-thickness defect resulted from ablation The depth to which ablation was necessary in each patient was evident from the presence and then absence of melanin pigment in the treatment area. It is necessary to differentiate melanin from the small areas of superficial charring which can occur during vaporization; the latter wash off easily with a chlorhexidine-soaked swab. The cavities that resulted from laser ablation were sprayed with povidone–iodine solution and dressed with dry dressings for 4–5 days

Results

Laser vaporization was an efficient method of ablating cutaneous and superficial subcutaneous metastatic melanoma. Between three and 450 lesions were ablated at

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Table 1 Site of primary tumours

Site	No. of tumours
Sole of foot	10
Dorsum of foot	7
Lower leg	61
Thigh	3
Perineum	1
Trunk	4
Upper limb	6
Head and neck	8

Table 2 M. D. Anderson stage on presentation

Stage	No. of patients
II	3
IIIa	53
IIIab	23
IV	21

Table 3 M. D. Anderson clinical staging of melanoma

Stage	Characteristic features
Stage 0	Superficial spreading melanoma
Localized primary melanoma	
Stage Ia	Primary intact
Stage Ib	Locally excised
Localized disease	
Stage II	Less than 3 cm from primary site
Regional metastases	
Stage IIIa	In-transit
Stage IIIb	Regional lymph nodes
Stage IIIab	In-transit and nodes
Systemic metastases	
Stage IV	Systemic disease

Table 4 Laser treatment

No. of treatments	No. of patients
1	24
2	27
3	13
4	12
5	5
6	6
7	5
8	2
9	1
≥10	5

Table 5 Interval between laser treatments

Treatments	No. of days between interval
1–2	64 (7–527)
2–3	58 (9–352)
3–4	74 (11–484)

Values are median (range)

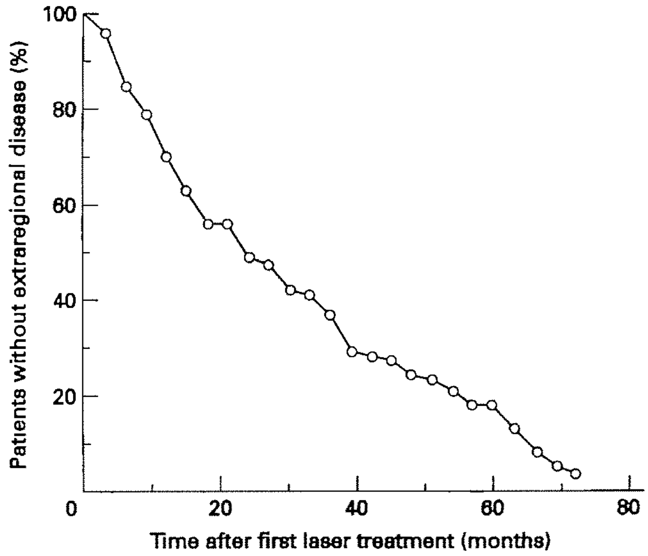

Fig. 1 Development of extraregional disease in patients who had stage I or III lesions at presentation

one time. In a typical patient 10–15 lesions would be ablated under local anaesthesia taking 15 min. Between 10 and 30 W continuous-wave laser power was used, the power selected being dependent on the size of the lesion to be treated. Patients reported little or no postoperative pain. Most lesions had formed a scab and could be left exposed within 1 week. Most wounds had healed completely within 6 weeks. Delayed wound healing occurred in one patient who had been referred after skin lesions had failed to respond to radiotherapy. A shallow ulcer, which took over 1 year to heal, developed over the medial malleolus after laser vaporization of a previously irradiated 1·5-cm lesion. Minor wound infections occurred in less than 3 per cent of the metastases that underwent laser therapy.

In total, the laser has been used to treat melanoma metastases on 377 occasions. The mean number of lesions ablated at each treatment was 17 (range 3–450). Less than 2 per cent of the lesions that underwent laser treatment recurred. New crops of metastases develop, however, necessitating further laser therapy. The overall number of treatments required by patients throughout the follow-up period is given in *Table 4*. The length of intervals between laser treatments are shown in *Table 5*. Of the patients with stage IIIa disease, 50 per cent were controlled by three or fewer laser treatments within the first year of follow-up and 64 per cent by four or fewer.

Thirteen patients who were initially managed with the laser developed large-volume subcutaneous disease and required ILP. These failures of laser treatment all had stage IIIa disease on presentation and had undergone between four and six laser treatments, with a mean interval between treatments of 50 days. Only six of the 13 patients showed a complete response to ILP, and five developed stage IV disease or died within 6 months.

Twenty-four (30 per cent) of the 79 patients in whom disease was initially limited to the limb of origin developed extraregional disease within 1 year despite local control (*Fig. 1*). Overall survival (*Fig. 2*) was 68 per cent at 1 year from first laser treatment with expected lower survival rates in patients with higher Anderson stage disease on presentation (*Fig. 3*).

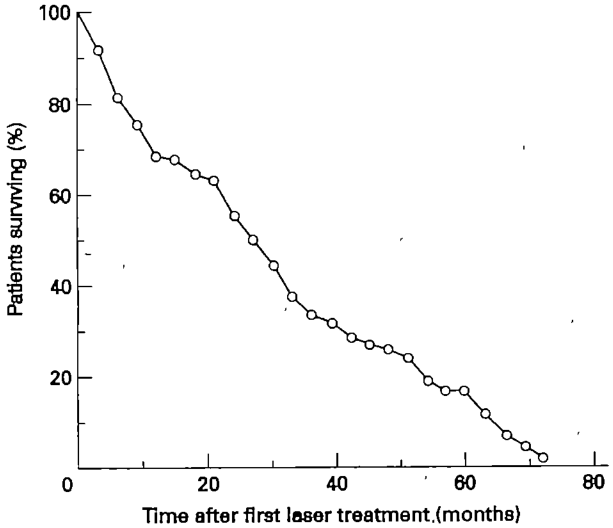

Fig. 2 Overall survival of patients treated with laser ablation

The probability of survival between the laser-treated patients with stage II and III disease on presentation was compared with that in a historical control group of 100 similarly staged patients treated by hyperthermic ILP at this hospital between 1979 and 1987. There was no significant difference between the groups, although the follow-up time for the patients having laser therapy was much shorter (*Fig. 4*).

Discussion

Several factors need to be taken into account when selecting the appropriate treatment for patients with stage III disease. First, overall survival is poor, approximately 50 per cent for those with stage IIIa lesions at 5 years[10–15]. Second, there is no evidence from the literature that a good response to ILP provides a survival advantage; occult distant metastases are liable to be present at the time of operation. Third, ILP is a major surgical

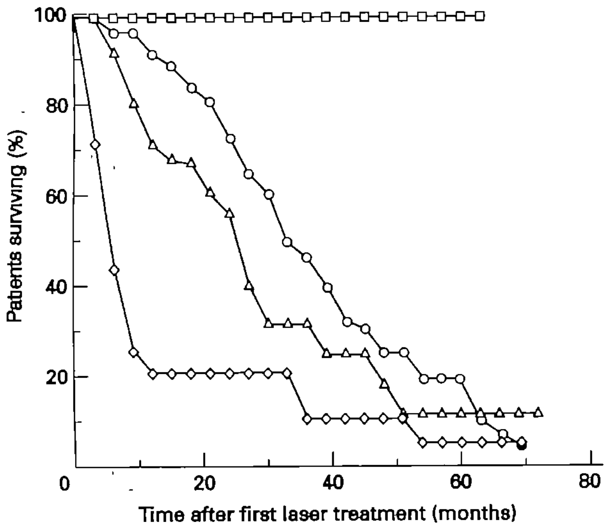

Fig. 3 Survival by M. D. Anderson stage on presentation. □, Stage I; ○, stage IIIa; △, stage IIIab; ◇, stage IV

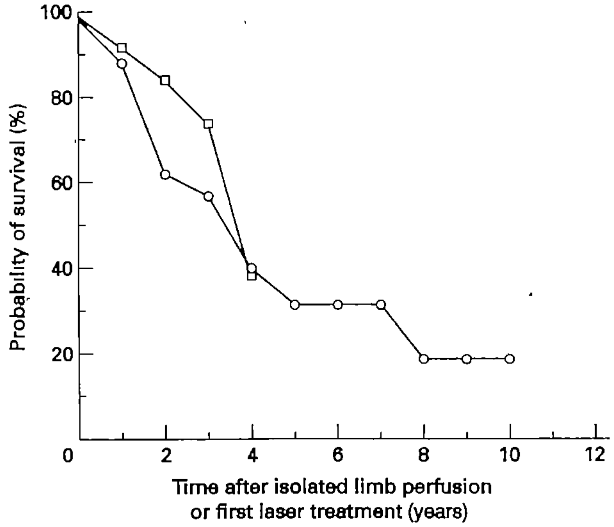

Fig. 4 Comparison of survival between patients undergoing laser treatment (□) and isolated limb perfusion (○)

Table 6 Published results of isolated limb perfusion

Reference	Year	Tumour stage	PR or CR	Objective response (%)	Duration of response (months)	Response rate at 5 years (%)	Survival rate at 5 years (%)
Krementz and Ryan[5]	1972	II	n.g.	n.g.	n.g.	58	62
		III	n.g.	n.g.	n.g.	46	47
Stehlin *et al.*[16]	1975	IIIa	n.g.	80	n.g.	n.g.	71·8
		IIIab/b	n.g.	80	n.g.	n.g.	48·2
Martijn *et al.*[17]	1981	II	n.g.	n.g.	n.g.	23	42
		III	n.g.	n.g.	n.g.	n.g.	46 (2 years)
Bulman and Jamieson[8]	1980	III	n.g.	49	17	n.g.	52
		IIIa	n.g.	49	6·7	n.g.	65·5 (3 years)
Ghussen *et al.*[18]	1984	II	n.g.	n.g.	16	n.g.	n.g.
		III	n.g.	n.g	23·2	n.g.	n.g.
Cumberlin *et al.*[19]	1985	II, IIIa	n.g.	n.g.	n.g.	n.g.	61
		IIIab/b	n.g.	n.g.	n.g.	n.g.	47
Lejeune *et al.*[6]	1989	II	n.g.	n.g.	n.g.	27	53·5
Skene *et al.*[7]	1990	II	n.g.	83·3	31·3	n.g.	n.g.
		III	n.g.	75·2	15·8	n.g.	n.g.

CR, complete response; PR, partial response; n.g., not given procedure with a significant morbidity rate, including oedema (76 per cent), pain (61 per cent), neuropathy (24 per cent), thrombosis (7 per cent), septicaemia (3 per cent) and thrombocytopenia (1·5 per cent)[1]. Comparison between the results of published series is difficult as the reported indications for ILP vary in different units with some performing the operation prophylactically, others at the first sign of in-transit metastases and some only when local disease cannot be controlled by multiple local excisions. Moreover, most reports fail to state the frequency of partial *versus* complete response, or duration of response (*Table 6*). All references to ILP in this paper refer to the technique using hyperthermia and melphalan. Recent reports on the use of melphalan with tumour necrosis factor α[20,21] have reported a higher initial response rate but results on duration of response are awaited.

In contrast to ILP, use of the carbon dioxide laser to ablate cutaneous and superficial subcutaneous lesions allows patients to be treated as day cases with virtually no morbidity. It is suggested that laser vaporization should be offered as the first-line treatment for suitable patients with stage IIIa disease. These would otherwise form the bulk of those considered for ILP. In this study 64 per cent of such patients were in remission at 1 year following four or fewer laser treatments. The carbon dioxide laser is also ideal for patients with stage IV disease which has spread to the skin.

Few experienced practitioners would disagree that among patients with stage IIIa disease melanoma exhibits a spectrum of biological behaviour. The rate of progression of in-transit disease is variable as is the rapidity of distant spread. Failure to manage by laser vaporization may be an indication of biological aggressiveness. Of the 13 patients initially treated by laser ablation but who failed to respond, only six have subsequently been controlled by ILP. The fact that laser treatment is not appropriate for every case of in-transit melanoma does not diminish its value for the majority.

The survival of patients with in-transit metastatic disease is poor and treatment should be effective and of low morbidity. Because of its simplicity and the natural history of the disease these data indicate that laser therapy is the treatment of choice for patients with non-nodal recurrence.

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Comparison of venous reflux in the affected and non-affected leg in patients with unilateral venous ulceration

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In 54 patients with unilateral leg ulceration of purely venous aetiology the only difference in venous reflux between affected and non-affected legs was with respect to the popliteal and crural veins. Deep and superficial venous reflux is common in legs without the skin changes typical of chronic venous insufficiency. The significance of venous reflux in an ulcerated leg cannot therefore be determined without reference to the contralateral, clinically normal, limb. Surgery should be directed at correcting reflux present in the ulcerated limb but not in the unaffected limb. In a minority of patients this entails superficial venous surgery alone, but in the majority such an approach would, ideally, entail correction of deep venous incompetence.

Although there are several well recognized causes of lower limb ulceration, venous disease is the most common aetiological factor. It is generally accepted that venous ulceration is usually a consequence of venous reflux, and less commonly of obstruction. The relative importance of reflux at different sites in the deep and superficial venous systems remains unclear[1–4]. The aim of the present study was to clarify this situation by defining a group of patients in whom ulceration was unilateral, in whom venous disease was the only identifiable factor, and in whom no major venous surgery had been performed. The pattern of venous reflux in the affected and non-affected leg was compared with colour flow duplex ultrasonography.

Patients and methods

Since 1985 approximately 1000 patients have been referred to the leg ulcer clinic of the Edinburgh Royal Infirmary. At first visit, clinical information relating to the ulcerated and non-ulcerated leg is recorded. In addition, since 1989, patients have had colour flow duplex ultrasonographic assessment of both legs. From this large, prospectively documented, population of patients with leg ulceration of varying aetiology, only 54 have been identified with the following characteristics: current ulceration confined to one leg; no current or previous ulceration or skin changes of chronic venous insufficiency in the other leg; no diabetes; ankle:brachial pressure index greater than 0·8 in both legs and no clinical evidence of significant arterial disease; no clinical or serological evidence of connective tissue disorder; no previous major venous surgery in either leg; and no evidence of a malignant aetiology to the ulcer. Major venous surgery included any operation more extensive than below-knee sclerotherapy or local stab avulsions. Application of these strict criteria clearly excluded the vast majority of patients with leg ulcers but has defined a population of patients whose ulcer would almost certainly be diagnosed as one of purely venous aetiology by most clinicians.

Colour flow duplex ultrasonography of the deep and superficial venous systems of both legs was performed by a single consultant radiologist (P.L.A.) using an Acuson 128 machine (Acuson, Mountain View, California, USA) and a 5- or 7·5-MHz transducer. Patients were examined standing, with a 30° head-up tilt. Venous reflux was elicited by means of manual calf compression and Valsalva manoeuvre in the upper thigh. Valsalva's manoeuvre was not used below the saphenofemoral junction. Reflux was considered pathological[5,6] if reverse flow exceeded 0·5 s.

Results

There were 26 men and 28 women of median age 69 (range 45–92) years; 26 ulcers were on the right and 28 on the left leg. The median duration of the current episode of ulceration was 7 (range 2–120) months; the median number of episodes of ulceration was 2 (range 1–20); and the median time since onset of first ulcer was 14 (range 1–43) years. Fifty-three ulcers were on the gaiter area and one on the foot. Ulcers were situated medially (36), laterally (14), anteriorly (two), posteriorly (one) and circumferentially (one).

There was no significant difference between ulcerated and non-ulcerated legs with respect to the pattern of venous reflux in the common femoral, proximal and distal superficial femoral, peroneal, long saphenous (groin and midthigh segments) and short saphenous veins (*Table 1*). By contrast, 42 ulcerated legs had proximal (above-knee) popliteal vein reflux compared with 31 non-ulcerated legs (χ^2 with Yates' correction $= 4{\cdot}53$, 1 d.f., $P = 0{\cdot}034$). Similarly, 39 ulcerated legs had distal (below-knee) popliteal vein reflux compared with 26 non-ulcerated legs ($\chi^2 = 5{\cdot}09$, 1 d.f., $P = 0{\cdot}024$). The above-knee popliteal vein was visualized in all patients and the below-knee popliteal vein in all but one. The proportion of uninformative scans was much higher when examining the crural veins, so that differences between ulcerated and non-ulcerated legs were more difficult to interpret. Nevertheless, ulcerated legs were also significantly more likely to have venous reflux in the posterior tibial (27 of 44 *versus* 16 of 47 informative scans; $\chi^2 = 5{\cdot}75$, 1 d.f., $P = 0{\cdot}016$) and anterior tibial (nine of 42 *versus* two of 44 informative scans; $\chi^2 = 4{\cdot}08$, 1 d.f., $P = 0{\cdot}044$) veins than legs unaffected by chronic venous insufficiency.

Discussion

This study demonstrates that deep and superficial venous reflux is common in legs clinically unaffected by the skin changes characteristic of chronic venous insufficiency. Thus the only significant difference between affected and unaffected legs was with respect to popliteal, anterior and

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Table 1 Patterns of venous reflux in ulcerated and non-ulcerated legs

	Ulcerated leg			Non-ulcerated leg			
Venous segment	Reflux	No reflux	Not seen	Reflux	No reflux	Not seen	*P**
Common femoral	45	8	1	42	12	0	n.s.
Superficial femoral							
Proximal	30	23	1	26	28	0	n.s.
Distal	27	24	3	23	29	2	n.s.
Popliteal							
Proximal	42	12	0	31	23	0	0·034
Distal	39	15	0	26	27	1	0·024
Tibial							
Posterior	27	17	10	16	31	7	0·016
Anterior	9	33	12	2	42	10	0·044
Peroneal	19	19	16	10	28	16	n.s.
Long saphenous							
Origin	37	6	11	36	8	10	n.s.
Midthigh	41	6	7	37	9	8	n.s.
Short saphenous (origin)	41	12	1	33	17	4	n.s.

*χ^2 test with Yates' correction; statistical analysis based on informative scans only; n.s., not significant

posterior tibial vein reflux. There was no difference in reflux at other sites within the deep system or in long and short saphenous incompetence.

While it is important not to neglect the overall severity of reflux, or even the severity of reflux in each segment, these observations suggest that the clinical significance of a particular pattern of venous reflux within a leg affected by chronic venous ulceration should not be determined without reference to the contralateral, clinically normal, limb. This may explain why studies that correlated the pattern of deep and superficial venous reflux with the severity of clinical disease have reported such variable results[7–10]. In addition, these results may explain why some clinicians report excellent medium-term healing from superficial venous surgery alone in up to 40 per cent of patients with ulceration[11,12], while others stress the poor long-term results of superficial venous surgery in the presence of deep venous incompetence[13,14]. For each patient there must be additional factors, perhaps at a microvascular level[15], which determine whether a particular pattern and severity of reflux leads to skin changes and ulceration. For example, it is common to see patients with gross superficial varicosities but without any skin changes. Similarly, in patients with the post-thrombotic syndrome there is a poor correlation between the pattern and severity of reflux and symptoms[1].

In the absence of a clear understanding of what these additional factors might be, or how to influence them, the surgeon must adopt a pragmatic approach. When contemplating surgery it would seem reasonable to advocate correction of reflux that is present in the ulcerated but not in the unaffected limb. In a minority of patients this entails superficial venous surgery alone. The present data confirm the results of earlier studies, from both this department[14–16] and others[17–20], demonstrating the importance of the popliteal vein in maintaining the clinical and haemodynamic normality of the calf. Although the consequences of correcting reflux within the popliteal segment have not been studied in this paper, the results suggest that developing reliable methods of doing so should be a surgical priority.

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Announcement

The Rouleaux Club

The Rouleaux Club is a society for surgical trainees who have an interest in vascular surgery. The club meets twice a year, once for a weekend meeting in summer and once at the Vascular Surgical Society in November.

The club provides a social setting where members meet and find mutual support especially in areas related to vascular research. The club is increasingly seen as the mouthpiece of vascular trainees and as such we wish to ensure that all trainees with a vascular interest have the opportunity to join.

All surgical registrars, research fellows or senior registrars with an interest in vascular surgery are invited to join the Rouleaux Club. Membership is free.

Please address all enquiries to: Mr Mark Whiteley, Secretary, The Rouleaux Club, Nuffield Department of Surgery, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK.

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Endovascular repair of abdominal aortic aneurysm: an initial experience

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Endovascular repair of abdominal aortic aneurysm (AAA) was attempted in ten patients over a 12-month period. Median age was 72 (range 61–82) years and median AAA diameter was 5·5 (range 5·2–6·0) cm. An aortoaortic (tube) graft was used in seven patients and a tapered aortoiliac reconstruction in three. There were two failures requiring conversion to open repair. Additional procedures included iliac artery angioplasty (two), coil embolization of an associated common iliac aneurysm (one) and femorodistal bypass (one). Median operating time was 162 (range 95–270) min and median blood loss was 1200 (range 800–2000) ml. Median hospital stay was 9 (range 5–21) days. Complications included death (one), reversible acute tubular necrosis (one) and prolonged ventilation (one). Postoperative evaluation with duplex ultrasonography and computed tomography demonstrated three perigraft leaks (two proximal and one distal). It is concluded that endovascular repair of AAA is feasible but is associated with significant complications and requires careful evaluation before widespread use.

Conventional elective abdominal aortic aneurysm (AAA) repair is associated with a mortality rate of approximately 5 per cent in many centres[1–5]. The risks of conventional repair increase in elderly patients and in those with coexisting cardiorespiratory disease[6]. An alternative approach to AAA repair involves insertion of a graft–stent combination via a peripheral artery, which is anchored to aorta of normal diameter above and below the aneurysm by its expandable metallic stents[7]. This avoids both laparotomy and aortic clamping and may be a safer alternative in high-risk patients[8]. The feasibility of this technique was first demonstrated in animal experiments[9–12] and recently several reports of initial clinical experience have emerged[13–17]. The authors' early experience with this technique using both tube and aortoiliac grafts is described.

Patients and methods

Patients were assessed before operation by means of computed tomography (CT), magnetic resonance imaging and intra-arterial digital subtraction angiography (with a calibrated catheter). Local ethical committee approval was obtained for this study and all patients gave written consent.

Endovascular grafts

The Endovascular Grafting System (Endovascular Technologies, Menlo Park, California, USA) was used in patients who had a sufficient proximal (more than 1·5 cm) and distal (more than 1 cm) aortic cuff to allow a tube graft repair. The catheter delivery system of this device comprises a coaxial unit that consists of a capsule containing the compressed graft, a retractable capsule jacket that permits graft delivery and a movable balloon catheter which is used to fix the stent hooks at the proximal and distal ends of the graft into the aortic wall (*Fig. 1*). This catheter-based delivery system is introduced via a 28-Fr sheath placed in the common femoral or iliac artery over a guidewire[15].

Patients with an insufficient distal aortic cuff or with aortoiliac aneurysm underwent endoluminal placement of a tapered aortoiliac graft combined with a femorofemoral bypass and embolization of the contralateral common iliac artery (*Fig 2*). This device consisted of a 4·2-mm diameter, 4-cm long Palmaz stent (Johnson and Johnson, Warren, New Jersey, USA) attached to a tapered polytetrafluoroethylene graft (Impra, Droitwich, UK). The graft–stent combination was mounted on a 3-cm diameter balloon dilatation catheter (Optiplast, Vas-cath, Ontario, Canada). This assembly was loaded into a 21-Fr sheath (Cook, Letchworth, UK) and introduced via a 24-Fr sheath in a manner similar to that of May *et al.*[14].

Implantation technique

The operation was performed under general anaesthesia in a fully equipped vascular operating theatre. All patients received heparin (5000 units) subcutaneously twice daily on the day before the procedure and this was continued until discharge. A further 5000 units heparin were administered intravenously at the start of the procedure. Through a groin incision a longitudinal common femoral arteriotomy was used to introduce the graft–stent combination. A 10-mm diameter Dacron (Meadox, Caddington, UK) graft was sutured end-to-side to the common iliac artery via a retroperitoneal approach in patients with a tortuous or narrowed common femoral artery and used as a temporary conduit as described by Parodi[7]. Accurate positioning of the endoluminal graft was performed under digital fluoroscopic control (Phillips BVM 29; Phillips Medical Systems, Best, The Netherlands) and stent deployment was aided by balloon inflation for 1 min at 2 atm (approximately 202 kPa) intraluminal pressure. During inflation of the balloon the mean arterial blood pressure was maintained at 80 mmHg. Angiography was performed on completion of the procedure to confirm successful exclusion of the aneurysm sac from the circulation. In patients with tapered aortoiliac grafts, the contralateral common iliac artery was occluded by stainless steel embolization coils (Cook). Retrograde angiography was performed to confirm successful occlusion. The contralateral leg was revascularized with a 10-mm diameter Dacron femorofemoral crossover graft.

After operation all patients were monitored for 24 h in the intensive care unit. A colour duplex scan and contrast-enhanced CT were performed before discharge from hospital to exclude perianastomotic reflux into the aneurysm sac. All patients were reviewed at 6 weeks and underwent physical examination, plain abdominal radiography, colour duplex scanning and contrast-enhanced CT. This sequence was repeated at 6 months and 1 year. Any abnormalities revealed by these investigations were further evaluated with angiography.

Results

Over a 12-month period from March 1994 to February 1995, 66 patients were assessed for endovascular repair;

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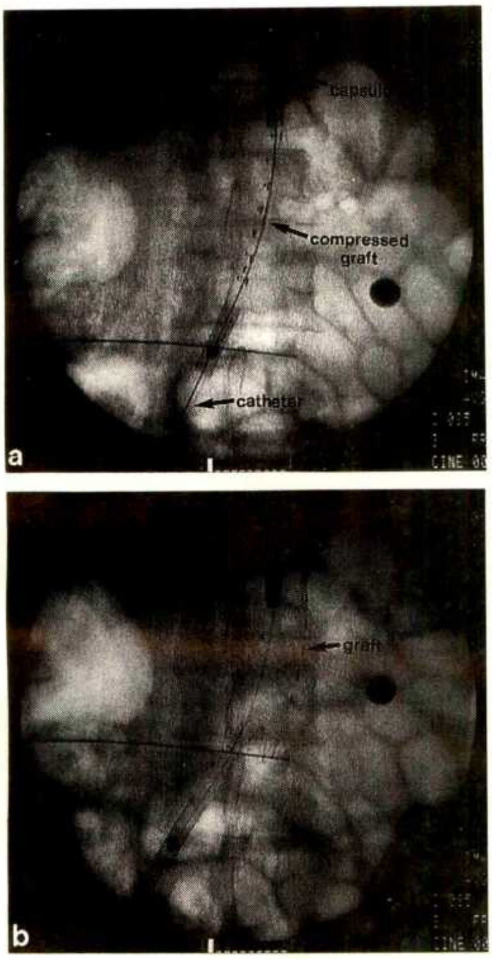

Fig. 1 Radiographic image of **a** the catheter delivery system containing a compressed graft. Note the radio-opaque markers positioned at the level of proximal and distal aortic cuffs. **b** Deployment catheter being withdrawn after deployment of the tube graft

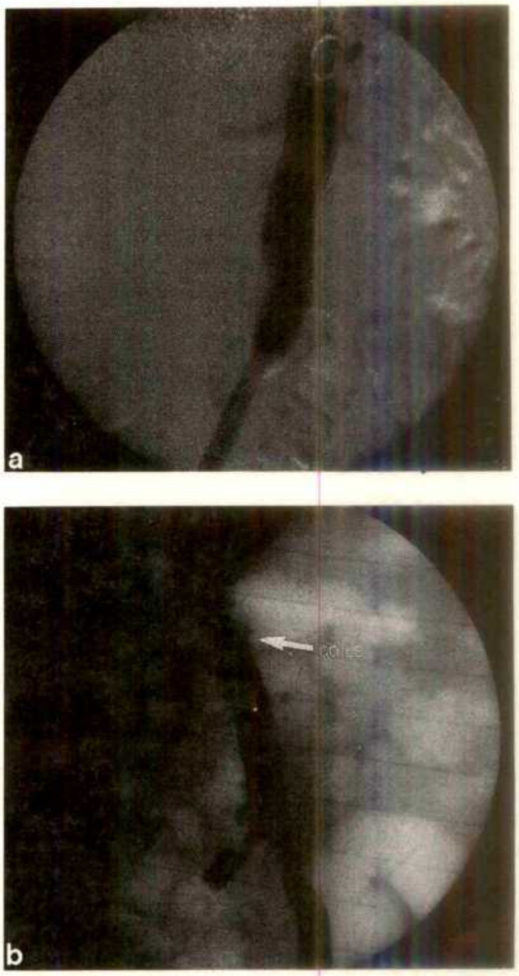

Fig. 2 Completion angiogram showing **a** a tapered aortoiliac graft and **b** coil embolization of the left common iliac artery

seven (11 per cent) were suitable for a straight graft repair. A further 23 (35 per cent) were suitable for a bifurcated graft repair. Endovascular repair was attempted in ten patients (nine men and one woman). Median age was 72 (range 61–82) years and median AAA diameter was 5·5 (range 5·2–6·0) cm. Preoperative risk factors included peripheral vascular disease in five patients, ischaemic heart disease in three, hypertension in two, diabetes mellitus in two and stroke in one. Three of these patients were considered poor candidates for conventional repair.

A tube graft repair was attempted in seven patients and a tapered aortoiliac reconstruction in three. Two patients in the latter group required conversion to an open procedure, one because of an iliac artery perforation produced during sheath insertion and the other because of graft migration from poor proximal fixation to the aortic wall. Both patients were considered 'fit' for open surgery which was carried out successfully. A temporary iliac conduit using a Dacron graft was constructed in seven patients to overcome narrow or tortuous common femoral arteries. In two a common iliac artery stenosis was encountered which required angioplasty to facilitate sheath insertion. One of the patients treated with a tube graft also had an isolated right common iliac aneurysm which was treated by coil embolization and a left-to-right femorofemoral crossover graft. Median operating time in those undergoing successful endoluminal repair was 162 (range 95–270) min. The patient with the procedure time of 270 min also required a right femorodistal vein bypass graft for rest pain and repair of bilateral, femoral aneurysms. Median blood loss was 1200 (range 800–2000) ml and six of the eight patients undergoing successful endovascular repair required blood transfusion.

Median hospital stay was 9 (range 5–21) days. Complications included death due to bronchopneumonia after microembolization and renal failure (one), reversible acute tubular necrosis (one) and prolonged ventilation (one). The patient who died had a history of myocardial infarction, congestive cardiac failure and stroke. The procedure was uneventful but 12 h after operation he developed an acutely ischaemic right leg requiring embolectomy and fasciotomy. The postoperative course was further complicated by renal failure and death from bronchopneumonia occurred 12 days after the procedure.

Postoperative evaluation with colour duplex ultrasonography and contrast-enhanced CT demonstrated a proximal leak (*Fig. 3*) in two patients and a distal leak in one. All leaks were encountered after a tube graft repair. One of the proximal leaks had resolved at 6 weeks' follow-up; the other persisted at 6 weeks. The distal leak was still

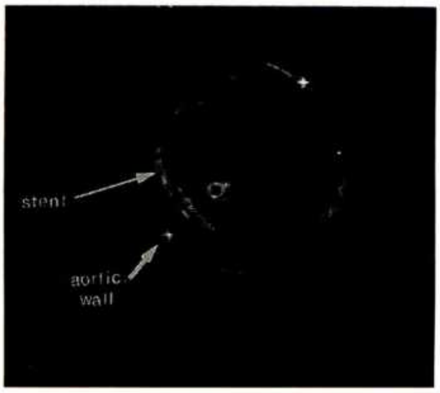

Fig. 3 Intravascular ultrasonographic image of an endoluminal graft showing incomplete seal at the proximal stent site

present at 6 months' follow-up, but there was no increase in the size of the aneurysm sac.

Discussion

Endovascular repair of AAA has been proposed as a less invasive alternative to conventional repair, particularly in patients with coexisting cardiopulmonary disease[8]. Although reports of initial experience from several centres suggest that this technique is feasible[13–17], various problems have been encountered that need further evaluation before its widespread application.

One of the most serious complications is microembolization[7,17]. This may cause multiorgan failure in the early postoperative period and is usually fatal. The exact mechanism of microembolization is not known, although it is thought that it may occur during guidewire or endoluminal graft manipulation within the aneurysm sac. This complication was encountered in one patient who died 12 days after the procedure. Balloon inflation at the level of the renal arteries during proximal stent deployment may also be a contributing factor. If the balloon encroaches over renal artery ostia, it may cause atheromatous debris to embolize into the kidney. Another important factor is the amount of contrast medium administered during these procedures. This may account for the transient renal failure in a patient in the present series, who was known to have left renal artery stenosis. The postoperative CT scan in this patient showed the stent to be well clear of the renal arteries.

Incomplete seal at the proximal or distal stent sites was present in three patients and was also encountered by Parodi[7], Moore and Vescera[15] and Chuter *et al.*[18]. This results in incomplete exclusion of the aneurysm from the circulation with potential continued aneurysm expansion. The authors' policy has been to observe these with regular colour duplex and contrast-enhanced CT scanning. Some of these may seal once the stent has been incorporated into the aortic wall. However, if the leak increases in magnitude or if there is an increase in the size of the aneurysm sac, further endovascular intervention or conversion to open repair is indicated. Although animal studies have shown incorporation of the stent into the aortic wall, there is no evidence that this also occurs in the atheromatous human aorta. Failure of stent incorporation may predispose to graft migration in the long term.

Another important problem is that of blood loss during the procedure. A sheath with a haemostatic valve was used for endoluminal tube graft insertion in the present series; despite this, there were considerable blood losses. Blood loss appears to occur mainly during guidewire or catheter exchanges. Blood replacement may increase the incidence of complications, and improvements in both devices and technique are necessary to minimize losses.

Parodi[19] attempted endovascular aneurysm repair in 65 patients between September 1990 and October 1994 with aortoaortic and aortoiliac grafts. He reported initial success in 84 per cent of aortoaortic implantations and in 75 per cent of aortoiliac procedures. Complications included microembolization in three patients, with incomplete seal in five (one proximal and four distal) and rupture as a result of a persistent leak in two. Similarly, in a series of 53 endovascular aneurysm repairs, May[20] had primary success in 43 patients; ten were converted to open repair due to a combination of stent migration, access problems, balloon malfunction and difficulty with deployment of bifurcated systems. Some 50 per cent of patients had vascular complications (femoral artery damage, proximal or distal perigraft leaks); 25 per cent had other systemic complications (renal failure, cardiac failure and stroke).

The aforementioned series and the authors' own early experience show that, although endovascular AAA repair is feasible, it is not without problems. The procedure may be long, complicated and associated with major blood loss. The conversion rate at present is about 15–20 per cent and so the technique may not be suitable for unfit patients.

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Short note

Side-effect of endovascular grafting to treat aortic aneurysm

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Recent experience of the treatment of six patients with aortic aneurysm using transfemoral placement of an endoluminal stent-supported graft has revealed some important side-effects.

Patients and methods

All patients were men between 65 and 78 years of age who were considered fit for open aortic surgery. Angiography and computed tomography revealed morphology suitable for an endovascular procedure, which was carried out in the operating theatre under fluoroscopy with road mapping by a team of vascular surgeons and radiologists Under general anaesthesia the femoral arteries were exposed bilaterally in all but one patient in whom one femoral artery was reached percutaneously. Heparin 5000 units was given systemically in all cases.

Results

Five of the six procedures were technically successful, resulting in aortobi-iliac (four patients) or straight aortic (one) grafts that performed well. In the sixth patient the device was inserted but the endoluminal graft could not be delivered because of an angled and calcified iliac artery, which caused damage to the introducer. The operation, therefore, was converted to an open procedure.

In two patients the introduction of the device into the aorta and manoeuvres unrelated to balloon occlusion of the vessel caused a sudden drop in blood pressure from a stable level of 120 and 95 mmHg respectively down to about 50 mmHg; fluid infusion and inotropic treatment raised the blood pressure, albeit slowly in one patient. Vasodilatation, in one instance a marked skin flush, occurred and the clinical picture resembled a septic reaction. No signs of myocardial ischaemia appeared in any patient. In one, a slight leakage was noted at the upper edge of the endoluminal graft.

All patients had a moderate temperature rise after the procedure. One patient reported a sudden pain in the thighs and some weakness in the legs 24 h after operation. Examination suggested an ischaemic neuropathy at the lumbosacral plexus level. The symptoms gradually disappeared with good resolution at 1 week. The first patient of the series also developed a left-sided leg weakness, with evidence of a plexus lesion, although this was difficult to interpret as there was also a femoral nerve compression due to groin haematoma.

Monocytes declined during the endovascular procedure, but were restored to normal by 6–24 h. The platelet count decreased in all patients. The inflammatory response to the treatment was investigated. Tumour necrosis factor (TNF) alpha levels increased rapidly in the two patients who showed a sudden drop in blood pressure (*Fig. 1*); this rise was accompanied by an upregulation of the adhesion molecule CD11c on granulocytes and monocytes. Terminal complement complexes showed increased levels 48 h after the endovascular procedure in these two

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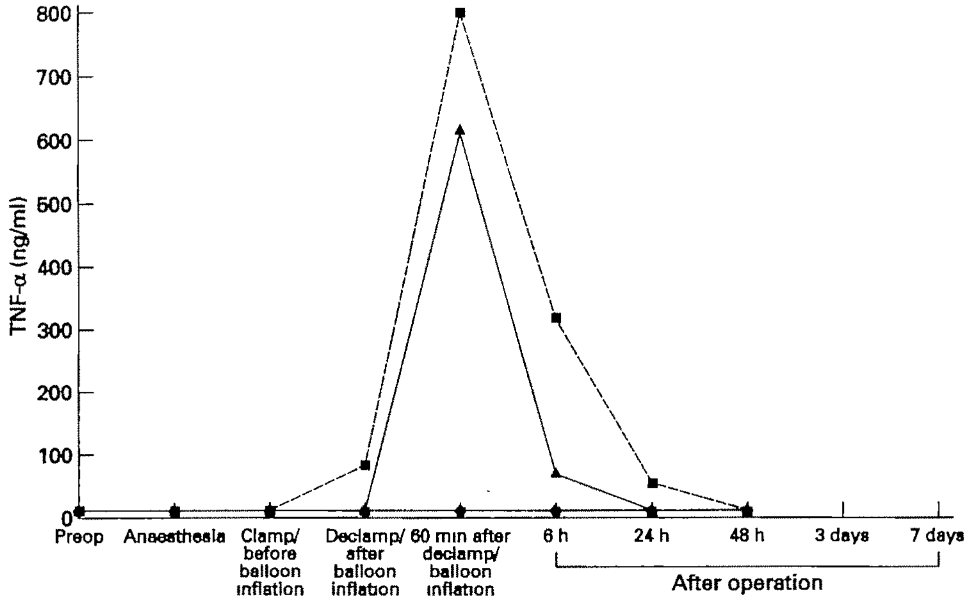

Fig. 1 Tumour necrosis factor (TNF) alpha levels during and after endovascular procedures in four patients. The peaks were noted in the two patients with severe peroperative blood pressure decreases

patients and were not restored until the seventh postoperative day in one.

Discussion

Endovascular procedures differ from conventional surgery in that the thrombotic content of the aneurysm is not removed. During the first few minutes after implantation, there might be some bleeding into the aneurysmal sac because of the comparatively high porosity of the graft. Pressure changes may occur in the sac. Furthermore, the large introducer (18–23 Fr) is manipulated into the aorta, and it is not possible to avoid touching the content of the aneurysm in many cases. These manipulations and events in the aneurysmal sac may cause cellular activation with cytokine release, clinically mimicking a septic reaction. Theoretically, the activation of granulocytes and monocytes may be more intense as they occur inside the blood stream with a high flow velocity. It is known that after open aortic surgery there is also a considerable inflammatory response and complement changes, the intensity varying in part with different graft surfaces (P. Swartbol *et al.*, unpublished results). Studies indicate that TNF is the prime cytokine released during the development of a systemic inflammatory response syndrome, and that TNF participates in the induction of capillary leakage in such a situation[1]. The explanation for the blood pressure decrease described may be cytokine release due to manipulation of the sac. Such blood pressure decreases have been noticed in other centres using various devices for endovascular treatment of aortic aneurysm, but no related laboratory data have yet been published. It seems less probable that a true septicaemia is induced.

Microembolization has been reported, mostly occurring in the feet. Parodi[2] presented an incidence of 7·5 per cent in his primary series. The nerve injuries described in the present series may have been caused by microembolization and an ischaemic lesion at the lumbosacral plexus level. The same mechanisms as for nerve lesions during open surgery may be expected, the most common explanation being ischaemia in the internal iliac territory. In this series all grafts ended above the origin of the internal iliac arteries, which were all open at completion angiography. Microembolization through these arteries cannot be excluded, and is probable in one case as there were also some microembolic stigmata in the corresponding gluteal area. Even microembolization via open lumbar arteries may have been possible.

Contrary to recent publications[3], we propose that, until the indications are fully established and potential problems have been elucidated and better understood, it is important to offer endoluminal treatment only to patients fit for open surgery; this should allow acutely occurring complications to be solved in relative safety. The aim is, of course, to find eventually an endovascular technique capable of safe use also in patients who are not candidates for open surgery. The best way to reach this goal is to conduct randomized controlled studies in patients in good general health, acceptable for open surgery and with a vascular morphology allowing endovascular therapy. Continuing studies on the inflammatory and immunological responses occurring during endovascular surgery may help to explain unexpected reactions.

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Surveillance imaging of the operated artery does not alter clinical outcome following carotid endarterectomy

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Clinical outcome was studied in 243 patients undergoing 260 carotid endarterectomies; 166 of these patients underwent serial postoperative surveillance imaging. Including perioperative events, cumulative freedom from ipsilateral stroke was 86 and 82 per cent at 5 and 10 years respectively; the mean incidence of ipsilateral stroke was 1·8 per cent per annum. Twenty patients (8 per cent) suffered cerebral ischaemic events in the hemisphere of the operated side during follow-up: eight transient ischaemic attacks (TIA) and 12 strokes (only two preceded by TIA). Two symptomatic patients were found to have occluded the operated artery but the remainder had no evidence of significant recurrent disease. Cumulative freedom from occlusion or severe (greater than 70 per cent) recurrent stenosis was 87 and 78 per cent at 5 and 10 years respectively; the mean incidence of recurrence of significant disease was 2·2 per cent per annum. No revisional surgery was performed on the operated arteries. In its current format, neither clinical nor surveillance imaging could have prevented any of the strokes observed during follow-up.

There is no consensus about the role of serial surveillance imaging after carotid endarterectomy (CEA). This prospective study examined patterns of disease recurrence in a cohort of 243 patients undergoing 260 CEAs over a 16-year period, in whom revisional CEA was only considered in symptomatic patients, enabling a valid assessment of natural history. The principal aim was to determine if a surveillance programme was justified in terms of yield, cost-effectiveness and ability to influence management decisions.

Materials and methods

Patients

Between January 1975 and December 1990, 243 patients underwent 260 CEAs. Before 1980, all data were collected prospectively and entered on to a standardized form. After 1980, data were recorded on a computer to which was added the earlier information. A full description of demographic data, clinical presenting features, concurrent diseases and risk factors have been detailed elsewhere[1]. In summary, 13 patients were asymptomatic at the time of undergoing CEA, 164 presented with a transient ischaemic attack (TIA) and/or amaurosis fugax, 11 with central retinal artery occlusion and 72 with completed stroke.

All patients underwent carotid angiography before surgery. The degree of stenosis in the operated internal carotid artery (ICA) was defined as the maximal biplane diameter reduction, expressed as a percentage of the normal ICA diameter above the stenosis. All angiograms performed since 1980 were interpreted by one observer (I.G.). Angiograms on patients undergoing CEA before 1980 were destroyed but had been scored previously in the same way. Twenty-three patients (9 per cent) had a stenosis of less than 25 per cent, 66 (25 per cent) of 26–50 per cent, 56 (22 per cent) of 51–74 per cent and 115 (44 per cent) of 75–99 per cent. Thirty-three patients (14 per cent) had a stenosis of more than 75 per cent or occlusion in the contralateral ICA.

Operation

All patients underwent CEA under normotensive, normocarbic general anaesthesia using systemic heparinization (5000 units). Before 1986 the carotid sinus nerve was anaesthetized with 1 ml 1 per cent lignocaine. After 1986 carotid sinus denervation was not practised. Between 1975 and 1980 arteriotomies were closed primarily ($n = 47$). After 1980 all arteriotomies were closed using patch angioplasty ($n = 213$), the majority with the long saphenous vein. Eighteen patients (7 per cent) suffered a stroke within 30 days of surgery. Nine (3·5 per cent) were disabling (three patients died) and nine (3·5 per cent) were minor. Six perioperative strokes followed ICA occlusion, which was confirmed at autopsy or re-exploration, or by angiography. There were no early complications related to patch angioplasty.

Follow-up and surveillance imaging

Patients were commenced on aspirin 150 mg daily unless contraindicated and reviewed in the vascular clinic at 4 weeks, 6 months and then annually until discharge at 10 years. Twelve patients (5 per cent) were excluded from long-term follow-up; three died after surgery, four were unable to attend clinic review (because of major perioperative stroke in three and prostate cancer in one) and five were completely lost to follow-up, despite letters to the family doctor. Thus follow-up data were available following 248 CEAs in 231 patients. Median duration of follow-up was 49 (range 2–120) months; 112 (45 per cent) were followed for 5 years or more and 33 (13 per cent) for 10 years. During surveillance, eight patients were lost to follow-up after a median of 24 (range 6–60) months. One emigrated, one was sectioned under the Mental Health Act and six could not be traced, despite letters to home and family doctor.

In 1983, all patients entered a revised protocol which now included serial assessment of the carotid bifurcation at 6 months and then annually after operation. Between 1983 and 1988, this was by intravenous digital subtraction angiography. All films were examined independently by one observer (I.G.) and the degree of restenosis determined as the maximal biplane diameter reduction, expressed as a percentage of the normal ICA diameter above the stenosis. After 1988, all new patients were serially assessed by colour duplex sonography and Doppler waveform analysis. A severe (greater than 70 per cent) stenosis was diagnosed on B-mode imaging criteria and a combination of either peak systolic velocity greater than 200 cm/s^2 or peak systolic velocity ratio (internal : common carotid) greater than

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2·5. Occlusion was assumed if colour imaging failed to reveal flow in the ipsilateral ICA. Only symptomatic patients were considered for formal carotid angiography during follow-up. Overall, 166 patients entered the imaging study, 129 prospectively from the outset (median follow-up 36 (range 6–84) months). Patients who had undergone CEA before 1983 were invited to enter the imaging study and 37 did so after a median of 60 (range 12–120) months of follow-up. The remainder declined, had died or had too far to travel.

Statistical analysis

Non-parametric statistical tests were employed. Data therefore refer to median and range. Cumulative patency and survival data were computed using the Kaplan–Meier method and based on clinical and/or imaging data relative to the time of death or last clinical/surveillance review. Study endpoints were: (1) death; (2) the development of cerebral ischaemic symptoms referable to the operated hemisphere (amaurosis fugax, TIA, stroke); and (3) recurrence of significant disease in the operated ICA (occlusion or stenosis greater than 70 per cent). All perioperative strokes and occlusions were included in the life-table calculations. Non-hemispheric symptoms were not considered statistical endpoints. The fate of non-operated, contralateral ICAs has been described elsewhere[3].

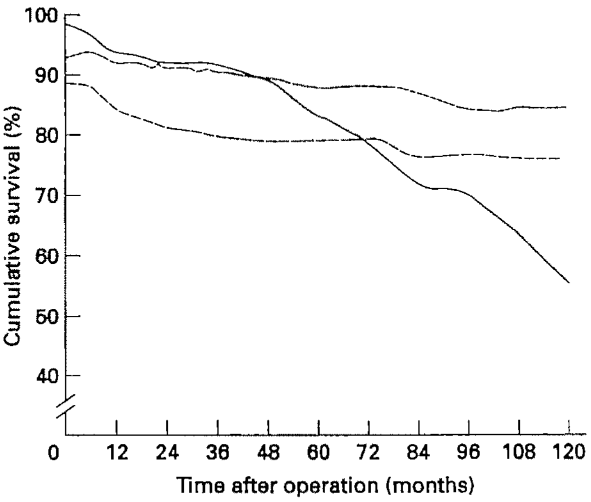
Results

Clinical outcome

Fifty-three of 243 patients (22 per cent) died during either operation ($n = 3$) or follow-up (*Table 1*). The commonest cause of late death was myocardial infarction. Only one patient died as a consequence of late cerebral infarction affecting the operated side. Post-mortem examination revealed thrombosis of the cavernous segment of the ICA in which there was a significant underlying atheromatous stenosis. There was, however, no significant recurrent disease of the cervical ICA. Overall, cumulative survival was 82 per cent at 5 years and 53 per cent at 10 years (*Fig. 1*).

Table 1 Causes of death during follow-up

Cause		No. of deaths
Perioperative		
Hypertensive encephalopathy		1
Cerebral infarction		2
Vascular		
Myocardial infarction		24
Stroke		3
Ipsilateral infarction	1	
Contralateral haemorrhage	1	
Brainstem haemorrhage	1	
Ruptured abdominal aortic aneurysm		1
Aortoduodenal fistula		1
Pulmonary embolus		1
Non-vascular		
Malignancy		8
Bronchogenic	6	
Breast	1	
Stomach	1	
Postgastric surgery		1
Bronchopneumonia		2
Liver failure		1
Suicide		1
Unknown		7



No. at risk			
Survived	221	116	39
Stroke-free	211	104	35
Event-free	199	98	33

Fig. 1 Cumulative survival (———), freedom from ipsilateral stroke (···), and freedom from any ipsilateral cerebral ischaemic event (----) following carotid endarterectomy

Twenty patients (8 per cent) suffered an ipsilateral cerebral ischaemic event during follow-up after a median of 23 (range 2–96) months. Eight presented with a TIA (ICA occlusion, $n = 1$; ICA normal or stenosis less than 50 per cent, $n = 4$; normal ICA but stenosed external carotid artery, $n = 1$; no imaging, $n = 2$); ten presented with an unheralded stroke (normal ICA, $n = 5$; cavernous ICA occlusion, $n = 1$; cervical ICA occlusion, $n = 1$; cervical ICA stenosis less than 50 per cent $n = 2$; no imaging, $n = 1$), and two presented with a stroke preceded by a TIA (neither had any significant recurrent ICA disease).

Cumulative freedom from any ipsilateral cerebral ischaemic event was 78 per cent at 5 years and 74 per cent at 10 years (*Fig. 1*). Cumulative freedom from ipsilateral stroke was 86 per cent at 5 years and 82 per cent at 10 years; the mean incidence of ipsilateral stroke was 1·8 per cent per annum (including all perioperative strokes). No patient in this series has undergone a repeat CEA of the operated ICA.

Surveillance imaging and outcome

Significant recurrent disease in the operated ICA. During the course of follow-up 15 of 166 arteries (9 per cent) undergoing serial imaging surveillance developed either occlusion ($n = 7$) or a severe (greater than 70 per cent) recurrent ICA stenosis ($n = 8$). Only one of the 15 vessels led to symptoms (TIA at 5 months) and was found to be occluded. Of the seven ICA occlusions, five were detected at the first 6-month surveillance study (all asymptomatic), and one patient entering the surveillance programme at 60 months had an asymptomatic occlusion. No patient progressed from a known recurrent stenosis to occlusion and no patient with a recurrent stenosis greater than 70 per cent ($n = 8$) has become symptomatic. Five other patients under surveillance have an asymptomatic recurrent stenosis of 50–70 per cent.

Including the known perioperative occlusions, cumulative patency (freedom from occlusion) was 91 per

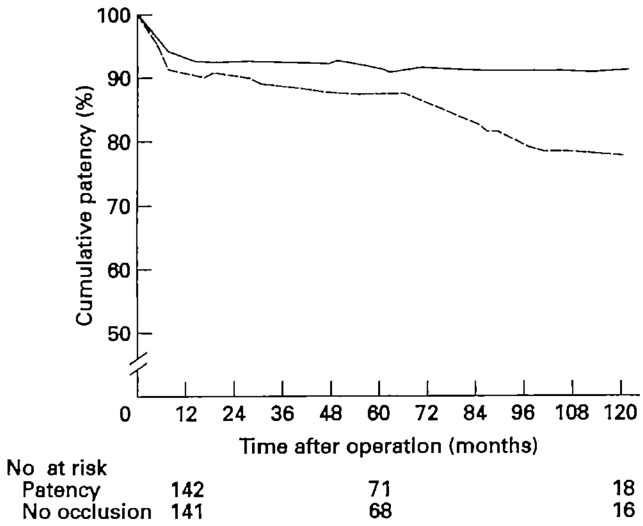


Fig. 2 Cumulative freedom from occlusion of the operated internal carotid artery (———) and cumulative freedom from occlusion and/or development of a recurrent stenosis of more than 70 per cent (– – – –) following carotid endarterectomy

cent at both 5 and 10 years (*Fig. 2*). Cumulative freedom from occlusion or severe stenosis (greater than 70 per cent) was 87 and 78 per cent at 5 and 10 years respectively (*Fig. 2*); the mean incidence of recurrence of significant disease was 2·2 per cent per annum.

This study demonstrated no increased cumulative 5-year risk of significant restenosis or occlusion in: (1) women (9 per cent) as opposed to men (11 per cent); (2) hypertensive (9 per cent) *versus* normotensive (10 per cent) patients; (3) patients initially presenting with TIA (7 per cent) as opposed to those with a stroke (17 per cent); and (4) patients undergoing primary closure (11 per cent) *versus* patch closure (15 per cent). This last observation is probably unreliable because of the small numbers of patients entering the serial surveillance study who had undergone primary closure.

Clinical outcome in the surveillance study. Ten patients (6 per cent) in the surveillance study developed ipsilateral cerebral ischaemic symptoms during follow-up. Four suffered a TIA and six had a stroke (none with an antecedent TIA). One patient who presented with a TIA became symptomatic following carotid occlusion before the first surveillance scan. None of the remaining nine patients had any evidence of disease progression from the preceding surveillance study and, in particular, none had a recurrent stenosis in excess of 50 per cent at the time of the onset of symptoms.

Discussion

The role of postoperative surveillance imaging after CEA is currently the subject of considerable debate, not least because of the logistical and financial implications should the projected increase in CEA operations materialize following publication of the recent international studies[4,5]. For any surveillance programme to be effective, there must first be a clinically important endpoint (e.g. late stroke). Second, the risk of stroke must be sufficiently high to justify surveillance. Third, there should be a clear association between late stroke and some reliable premonitory feature (e.g. antecedent TIA or disease recurrence). Fourth, the method of surveillance should reliably (and cost-effectively) identify those at risk of suffering a late stroke. Finally, there must be an effective means of treatment (e.g. repeat CEA). However, it has become difficult to analyse the effectiveness of current surveillance programmes because much of the data presented are proportional or descriptive, and differing definitions, patient selection criteria, endpoint criteria and follow-up periods add to the complexity.

After a successful CEA, up to 30 per cent of patients (averaging 9 per cent) will suffer further cerebral ischaemic events during follow-up[6–13], the majority occurring 12 months or more after surgery[6–8,10]. This translates into a cumulative annual risk of 2·8–5·6 per cent for any ipsilateral cerebral ischaemic event[6,7]. However, the principal aim of a surveillance programme is not the prevention of transient events, but the prevention of unheralded stroke. While it is not disputed that late stroke is an important endpoint to prevent, this study has shown that the mean annual incidence of ipsilateral stroke after CEA is only 1·8 per cent (including perioperative strokes), which is similar to the 1–2 per cent rates published elsewhere[6,9,14,15]. In addition, there is evidence that the risk of stroke may be higher in patients with late recurrent disease as opposed to those with recurrent stenoses developing within the first 3 years after surgery[16]. It must be accepted that the risk of late stroke is both low and distributed over time (*Fig. 1*). This suggests that a surveillance programme would need to be very sensitive and continued indefinitely after operation to be completely effective.

However, if late stroke (despite its low incidence) were preceded by some reliable premonitory feature, surveillance might be effective. At present, surveillance is primarily limited to regular clinical review, with or without serial imaging of the carotid bifurcation. The principle underlying clinical review is the assumption that strokes are preceded by transient ischaemic events which can be elicited from patients by regular history taking[17]. In this study, however, only two of 12 patients with late stroke had an antecedent TIA. This limitation has been well described by others[6,8,9,12,15,18] and accords with the 15–20 per cent prevalence of antecedent TIA observed in the natural history of ischaemic stroke in the community at large[19]. In the present cohort of patients, regular clinical surveillance alone would not be expected to have prevented any of the observed strokes. Moreover, because the majority of patients with recurrent TIAs were referred to the vascular clinic outwith routine annual or 6-month appointments, it might have been just as effective to offer an open-door policy of rereferral to the patient or family doctor.

The impetus behind the introduction of surveillance imaging came from reports in the literature suggesting that up to 36 per cent of patients (averaging 13 per cent) developed occlusion or a recurrent ICA stenosis greater than 50 per cent during follow-up[6–10,12,13,18,20], although fewer (9–12 per cent) progressed to occlusion or a more severe (greater than 70 per cent) stenosis[21,22]. Alarming as this may seem, a review of actuarial data shows that the mean annual risk of developing severe recurrent disease is only 2–3 per cent[7–9]. The rationale for undertaking prophylactic revisional carotid surgery for recurrent (usually asymptomatic) ICA stenosis arose from either conviction or evidence from non-actuarial data that patients with recurrent stenosis were more likely to suffer ischaemic events than those with normal or minimally diseased vessels. While there is some evidence that up to 67 per cent of patients (averaging 26 per cent) with a recurrent stenosis of greater than 50 per cent may suffer late ischaemic events[6,7,9,10,18,21,23–31] as compared with only 4–17 per cent of patients (averaging 11 per cent) with a recurrent stenosis of less than 50 per cent[6,18,21,32], this is not reflected in differences in cumulative stroke risk. A number of studies have now reported that the cumulative 5- and 10-year risk of ipsilateral stroke is no different in patients with and without significant recurrent disease[6,8,9,18,21,23,33]. Indeed, some studies have suggested that patients with significant stenosis may actually have a lower cumulative stroke rate[8,34]. In the present study, only one of the patients with late symptoms in the surveillance programme had significant recurrent disease.

This surveillance programme, therefore, failed to prevent any late stroke and did not alter the clinical management of any patient. This conclusion applies also to the non-operated, contralateral artery[3]. This observation, while disappointing, accords with the experience of others who have observed that surveillance imaging is both expensive ($25 000–$100 000 per stroke prevented[8,15]) and has only a small probability of influencing management decisions (2–3 per cent[8,10,15]). The cumulative annual risk of late stroke is low: 1·4 per cent in the non-operated hemisphere and 1·8 per cent in the operated hemisphere. The likelihood of requiring a revisional CEA is remote[6,7] and there is no clear evidence that a recurrent stenosis of greater than 50 per cent confers any greater risk of late stroke than a lesser stenosis. Therefore, any surveillance imaging programme based on simply recognizing the degree of stenosis is unlikely to be either clinically useful or cost-effective.

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Case report

Delayed pancreatoduodenectomy followed by delayed reconstruction for trauma

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Abdominal packing is frequently used as a temporary measure to control bleeding in patients with severe intra-abdominal haemorrhage accompanied by coagulopathy, hypothermia and acidosis[1,2]. Pancreatic resection followed by delayed reconstruction has been performed successfully in trauma[3]. A case is reported of delayed pancreatic resection and delayed reconstruction for a gunshot wound to the abdomen.

Case report

A 15-year-old boy was brought to the emergency room with a single gunshot wound in the epigastrium. The exit wound was located on the back just to the right of the second lumbar spinous process. The patient was hypotensive. Resuscitation was commenced and he was taken to the operating theatre. A resuscitative left anterior thoracotomy with cross-clamping of the descending thoracic aorta was performed. At laparotomy the patient had a massive haemoperitoneum, with injuries to the second part of the duodenum, head of pancreas and intra-pancreatic portion of the common bile duct, together with the right renal artery and the renal vein at its junction with the inferior vena cava. Right nephrectomy was combined with repair of the inferior vena cava in the form of a venorraphy. By now the patient had developed hypothermia, coagulopathy and acidosis. To shorten the surgical procedure, the injured portion of the duodenum was excised, the distal stomach and second portion of the duodenum were closed with a stapler and the distal common bile duct was ligated. The abdomen was packed, and the patient was taken to the surgical intensive care unit.

After resuscitation over the next 30 h, the abdomen was re-explored. The patient underwent pancreatoduodenectomy with stapled closure of the distal stomach and proximal jejunum, cholecystectomy and drainage of the common bile duct, gastrostomy, feeding jejunostomy and ligation of the occluded inferior vena cava. Two large closed suction drains were placed close to the pancreas. The postoperative course was complicated by the development of a biliary leak (requiring percutaneous placement of a stent through the left hepatic duct), pancreatic fistula, adult respiratory distress syndrome requiring 4 weeks of ventilatory support, and intra-abdominal abscess requiring percutaneous drainage guided by computed tomography

Planned reconstruction was performed 10 weeks after pancreatoduodenal resection. A side-to-side gastrojejunostomy and an end-to-side choledochojejunostomy were performed The pancreas was not anastomosed. The abdomen was closed with polyglactin mesh and later required skin grafting. The patient was discharged 4·5 months later on a regular diet with pancreatic enzyme supplements but with no evidence of diabetes mellitus.

Discussion

In patients with severe blood loss, several recent studies have stressed the need to limit the initial operative procedure to the arrest of major bleeding, the control of spillage of gastrointestinal secretions and urine, and the correction of coagulopathy, hypothermia and acidosis.

The management of pancreatoduodenal trauma is complex and is dictated by the condition of the patient, the severity of the pancreatoduodenal injury itself and the nature of associated injuries. Since the first reported case in 1961, 186 cases of pancreatoduodenectomy for trauma have been reported[4]. Of these, only one patient had undergone delayed pancreatic reconstruction, 36 h after the initial resection. The present patient underwent pancreatoduodenectomy 30 h after the initial damage-control laparotomy, and planned reconstruction 70 days later. Pancreatoduodenectomy continues to be an important therapeutic option for severe pancreatoduodenal injury[5].

Principles of management in haemodynamically unstable patients include control of haemorrhage as a first priority. Major resections such as pancreatoduodenectomy can be delayed until the patient is stabilized. Further reconstruction can be delayed until recovery from critical illness.

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Adrenalectomy for metastatic disease to the adrenal glands

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A policy of supportive treatment is frequently adopted for patients with metastatic disease to the adrenal glands. This study reports an experience with adrenalectomy for adrenal metastasis. Between 1983 and 1993, adrenalectomy was performed in 52 patients for metastasis to the adrenal glands. Survival was calculated by the Kaplan–Meier method and compared with the log rank test. Primary tumour sites included kidney ($n = 15$), lung ($n = 11$), colon ($n = 7$), unknown ($n = 5$), stomach ($n = 3$), melanoma ($n = 3$) and other ($n = 8$). Adenocarcinoma (69 per cent) was the most common histological cell type. Thirty-two patients were asymptomatic on initial evaluation. Symptomatic adrenal pain relief was achieved in 11 of 13 patients. Overall survival rates were 73 per cent at 1 year and 40 per cent at 2 years. Patients with potentially curative resection had better survival than those who had a palliative procedure. Patients with adrenal metastases due to adenocarcinoma had improved survival compared with that in those with other histological cell types. Although long-term survival is generally poor, highly selected patients with adrenal metastasis (symptomatic disease or adenocarcinoma) may benefit from surgical resection.

Metastasis to the adrenal glands is frequently found at autopsy[1–4]. With continuing progress in imaging techniques, particularly computed tomography (CT), increasing numbers of adrenal metastases have been detected before death or incidentally at the time of presentation of non-adrenal malignant disease[5–10]. The discovery of adrenal metastasis in patients with clinically operable primary tumours automatically transfers these patients to an advanced disease stage and a non-operative strategy is usually employed[5–7]. The adoption of aggressive surgical resection for solitary adrenal metastasis remains controversial, despite occasional long-term survival described in many single case reports or small series. The reported site of origin of surgically resected adrenal metastasis includes renal cell carcinoma, non-small cell lung carcinoma, malignant melanoma, colorectal carcinoma, follicular thyroid carcinoma and hepatocellular carcinoma[11–24]. This study reports a relatively large number of patients who underwent surgical resection for adrenal metastases at a single institution.

Patients and methods

A retrospective review of patients undergoing adrenalectomy between 1983 and 1993 revealed 65 patients with metastatic disease in the resected specimen. Histological slides were subjected to a repeat review by a single pathologist, which resulted in the exclusion of 13 patients who had either direct extension of the tumour in the gland without true metastasis, or incidental ipsilateral gland metastasis found during radical nephrectomy

Patients with adrenal metastasis diagnosed or treated at the same time or before that of the primary tumour were classified as having synchronous disease. Those diagnosed at least 12 months after treatment of the primary tumour or shown to be absent at the time of treatment of primary tumour were classed as metachronous. Survival was evaluated with Kaplan–Meier methods[25] and compared between different groups by log rank testing[26]. The endpoint for survival analysis was death from any cause.

Results

Demographic data

There were 34 men and 18 women of median age 59 (range 35–77) years.

Pathological findings

Histological analysis of the resected adrenal gland was compared with that of the primary tumour whenever possible. The site of origin of the primary neoplasm is shown in *Table 1*. Of the 11 primary lung cancers, five each were adenocarcinoma and large cell carcinoma, and one was a small cell carcinoma. Of the 15 patients with renal cell carcinoma, nine had contralateral metachronous metastasis, three ipsilateral metachronous and three contralateral synchronous tumours.

Histological findings of the adrenal metastases are given in *Table 2*. Of five patients with no antecedent history of malignancy and no identifiable primary tumour, histological examination revealed adenocarcinoma in four and small cell carcinoma in one. There was no clinical or radiological evidence of lung primaries, although four had suggestive histological features.

Resection for bilateral metastases was performed in four patients. Median size of the metastases was 6·5 (range 1–15) cm.

Clinical features

Mean time from diagnosis of primary tumour to treatment of adrenal metastasis was 30 (median 19, range 0–102) months. Some 17 patients had a synchronous presentation of both primary tumour and adrenal metastasis. No operative procedure was performed for the primary tumour in ten patients: five with an unknown primary site; three with lung carcinoma, one with malignant melanoma and one with prostatic cancer. Chemotherapy was given to the three patients with carcinoma of the lung after adrenalectomy before the primary tumour was found to be irresectable at thoracotomy. The primary tumour could not be located in

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Table 1 Site of origin of 52 primary tumours

Organ	No. of patients
Kidney	15
Lung	11
Colon	7
Unknown (four ACs and one SCCA)	5
Skin (malignant melanoma)	3
Stomach	3
Urinary bladder	2
Uterus (leiomyosarcoma)	2
Breast, prostate, gallbladder (SQCC), MFH	1 each

AC, adenocarcinoma; SCCA, small cell carcinoma; SQCC, squamous cell carcinoma; MFH, malignant fibrous histiocytoma

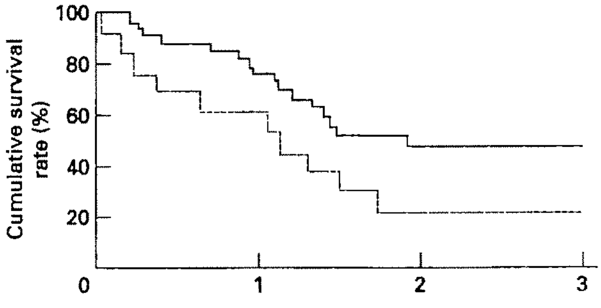
Table 2 Histological cell type in 52 tumours

Histological cell type	No. of patients
Adenocarcinoma	36
Large cell carcinoma	5
Malignant melanoma	3
Sarcoma	3
Small cell carcinoma	2
Transitional cell carcinoma	2
Squamous cell carcinoma	1

Table 3 Primary indications for operation

Indication	No. of patients
Clinical solitary metastasis	30
Adrenal pain*	13
Incidental adrenal mass	1
Unknown	8

*Eleven patients also had clinical solitary metastasis



No. at risk	0	1	2	3
Curative	38	25	11	7
Palliative	14	8	2	1

Fig. 1 Survival curves for patients who underwent either potentially curative ($n = 38$; ——) or palliative ($n = 14$; ———) resection $P = 0{\cdot}029$ (curative *versus* palliative operation, log rank test)

the patient with malignant melanoma, while hormonal therapy was employed for the patient with primary prostatic cancer. Fourteen patients had an antecedent history of distant metastasis to other sites that were treated by surgical resection or chemotherapy before resection of the adrenal metastases. This occurred most commonly in patients with renal cell or colorectal carcinoma.

All lesions were detected and localized by CT and 32 patients, who did not have symptoms referable to adrenal metastasis, were diagnosed by routine tumour screening or follow-up surveillance. One patient with an occult primary tumour presented with an incidental adrenal mass during investigation for refractory hypertension. In 19 patients a combination of symptoms including pain, weight loss, or systemic symptoms alerted the physician to the possible presence of metastasis. Two patients with bilateral adrenal metastasis presented with symptoms of adrenal insufficiency which was documented biochemically. CT-guided fine-needle aspiration biopsy performed in 27 patients before operation was accurate in 22. The primary indications for adrenalectomy are shown in *Table 3*.

Operative details

Adrenalectomy was performed via the posterior lumbar approach in ten patients and via the anterior transabdominal approach in 42, with concomitant resection of other organs in 14 patients: splenectomy (nine), nephrectomy (three), bowel resection (three), distal pancreatectomy (two), hepatic segmentectomy (one) and resection of a portion of the diaphragm (one). Potentially curative resection was achieved in 38 patients.

There was one perioperative death and four patients developed major morbidity (myocardial infarction, intravenous catheter sepsis, intra-abdominal abscess and disseminated intravascular coagulopathy). Chemotherapy was given to six patients, radiotherapy to four and interferon to four with renal cell carcinoma.

Follow-up and survival

Symptomatic relief with respect to adrenal pain was achieved in 11 of 13 patients over a mean period of 18 (median 13) months. Median survival in this group of symptomatic patients was 14 months. The contralateral adrenal gland was resected for metastatic disease in three patients at 7, 8 and 12 months after initial adrenalectomy. At the time of follow-up, ten patients remain well without evidence of disease, 12 are alive with metastasis and 30 have died from malignancy. Of the survivors, median follow-up was 22 months (range 1 month to 8·9 years). One patient was lost to follow-up 1 month after operation with evidence of metastasis. All survivors were followed up within 12 months from the study (73 per cent within 6 months). Overall actuarial survival rates were 73 per cent (95 per cent confidence interval (c.i.) 61–86 per cent) at 1 year and 40 per cent (95 per cent c.i. 25–56 per cent) at 2 years. Overall median survival was 13 months for those who died (range 1 month to 8·6 years). When patients with primary tumours from different sites of origin were compared, there was no significant difference in survival rates ($P = 0{\cdot}09$), but patients with potentially curative resection ($n = 38$) had a better survival rate than those who had a palliative operation ($n = 14$) ($P = 0{\cdot}029$) (*Fig. 1*). Patients with adrenal metastasis due to adenocarcinoma had a significantly improved survival rate compared with that in patients with other histological cell types (51 *versus* 18 per cent at 2 years respectively, $P = 0{\cdot}0015$). Even when patients with potentially curative resection were considered alone, the survival advantage of patients with adenocarcinoma ($n = 29$) over those with other cell types ($n = 9$) persisted ($P = 0.022$).

Discussion

Metastasis to the adrenal glands for patients with epithelial malignancy is a relatively common finding in many autopsy series[1-4]. Many adrenal masses including metastases are being detected incidentally by CT, and with increasing frequency. Prospective CT studies have detected adrenal metastasis in up to 32 per cent of patients with bronchogenic carcinoma at initial presentation[5-7]. Surgical treatment for metastasis to the adrenal glands has not been widely adopted because of the concern about probable associated advanced diffuse metastatic disease. Aggressive surgical resection, however, of a clinically unsuspected adrenal metastasis may translate into survival benefit and potential surgical cure for a truly solitary early metastasis[11-14]. Long-term survivors after surgical treatment for adrenal metastasis have been reported[11-18].

The present study showed that surgical resection for metastasis to the adrenal glands was associated with rare mortality and acceptable morbidity rates. The prognosis of these patients depends on multiple factors such as the site of origin and histological cell type of primary tumours, antecedent history of distant metastasis or discovery of other synchronous distant metastasis, and extent of local disease. It is logical that an important criterion for successful surgical resection would be the presence of truly solitary metastatic disease. The majority of patients in this study had apparently localized solitary adrenal metastasis and patients with potentially curative resection had a better survival rate than those who underwent a palliative procedure. Interestingly, patients with adenocarcinoma metastatic to the adrenal glands had improved survival compared with those with other histological cell types, but this may represent a quirk of limited numbers. Nearly all patients in this series probably represent a highly selected subgroup with tumours that were biologically more indolent. To what degree the procedure influenced survival in these patients can only be speculated but similar aggressive resection for metastatic disease has achieved limited success in hepatic and pulmonary resections for metastatic colonic[27] and islet cell carcinoma, sarcomas[28] and carcinoids[29]. Identification of factors that may predict survival benefit would seem to be the next challenge.

In patients with symptomatic disease such as pain, adrenalectomy may achieve significant pain relief as well as curative treatment. Soffen *et al.*[30] showed that the overall response rate was 75 per cent in 16 patients receiving palliative radiotherapy for painful adrenal metastasis; median survival was only 3 months in this group of patients. Although symptomatic adrenal metastasis accounted for only 25 per cent of this series 85 per cent had complete or partial pain palliation over a median period of 13 months. Median survival in this group of patients was 14 months.

Only ten patients underwent posterior adrenalectomy. Many patients exhibit a troublesome periadrenal 'reaction' which complicates the dissection and makes the space-confining posterior approach particularly difficult and potentially hazardous. This phenomenon and the need, at times, for critical assessment of the remainder of the peritoneal cavity makes the anterior approach the procedure of choice.

Multidisciplinary consultation followed by careful patient discussion should allow selection of patients who are most likely to benefit from surgical treatment. In this study, surgical resection for adrenal metastasis was associated with rare mortality and low morbidity rates. It offers temporary but effective pain relief and may result in survival benefit in selected patients.

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Early postoperative plasma calcium concentration as a predictor of the need for calcium supplement after parathyroidectomy

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This study evaluated early postoperative serum calcium concentration as a predictor of hypocalcaemic symptoms and the need for calcium supplements. A total of 64 consecutive patients undergoing curative parathyroidectomy for primary hyperparathyroidism were studied. Twenty patients (31 per cent) developed hypocalcaemic symptoms requiring calcium supplements. Plasma calcium levels in the preoperative and early postoperative periods were similar in patients who required calcium supplements and those in whom they were not necessary. There was no significant difference in the percentage decrease in early calcium levels after operation between the two groups. In those undergoing reoperative surgery and subtotal parathyroidectomy the percentage decline was significantly higher in patients who required calcium supplements (12·8 *versus* 5·6 per cent, $P<0·005$). A fall of 10 per cent or more was consistently followed by hypocalcaemic symptoms. Calcium determination in the early postoperative period is of little value in predicting the onset of hypocalcaemic symptoms.

Temporary and permanent hypocalcaemia are recognized complications after surgery for primary hyperparathyroidism. Incidence varies from 13 to 46 per cent[1–4]. Postoperative hypocalcaemia may be due to removal of excessive, or all, parathyroid glands, ischaemic injury, long-term suppression of non-adenomatous parathyroid glands or the hungry bone syndrome. While daily monitoring of plasma calcium concentration after parathyroid surgery will detect hypocalcaemia, the value of a plasma calcium determination 4–6 h after operation is debatable[3]. Significant hypocalcaemia usually occurs 24 h after surgery[2,3]. There is little information on measurements in the early postoperative period. This study evaluated whether early plasma calcium measurement predicted the onset of hypocalcaemia and the need for calcium supplements.

Patients and methods

Some 64 consecutive patients undergoing curative parathyroid surgery for primary hyperparathyroidism were studied. Patients with secondary or tertiary hyperparathyroidism, or persistent hypercalcaemia after exploration were excluded from the analysis. The following data were collected: sex and age, histology and weight of the resected diseased parathyroid gland; preoperative plasma albumin level and plasma calcium concentration. Plasma calcium concentration was measured before surgery, 4–6 h after surgery and on the first and subsequent mornings after operation. Onset of hypocalcaemic symptoms and treatment were documented. Plasma calcium concentrations were corrected to an albumin level of 42 g/l with a normal range of 2·25–2·7 mmol/l. Plasma calcium concentration was measured by a colorimetric method using an automated analyser (BM/Hitachi 717; Boehringer Diagnostica, Mannheim, Germany).

All surgical procedures were carried out by one surgeon and a bilateral neck exploration was practised. If a parathyroid adenoma was found and confirmed on frozen section, this was resected with a half biopsy of one of the three other normal glands. If parathyroid hyperplasia was found, a subtotal parathyroidectomy (3½ glands resection) was carried out. Patients were warned of the possibility of postoperative hypocalcaemic symptoms. Calcium supplements were prescribed if patients developed hypocalcaemic symptoms regardless of the plasma calcium level or when plasma calcium concentration decreased below 2·00 mmol/l (less than the lower limit of normal range, and chosen because patients often become symptomatic with normal values after parathyroid surgery). The patients were divided into two groups based on whether or not calcium supplements were given in the first week after operation. The two patient groups were compared with regard to plasma calcium concentration and the decrease in calcium levels in the evening (4–6 h after surgery). Comparison was also made with regard to the weight of resected glands

Results are expressed as mean(s.e.m.) and data compared using Student's t test. Correlations were studied with linear regression using Pearson's correlation coefficient. Statistical significance was taken at $P<0·05$.

Results

The clinical and biochemical characteristics of the 64 patients are shown in *Table 1*. Female: male ratio was 5:1. Seven patients underwent re-exploration for either persistent or recurrent hyperparathyroidism and eight patients had subtotal parathyroidectomy for parathyroid hyperplasia. Twenty patients (31 per cent) required calcium supplements after surgery; nine on the first, six on the second, four on the third and one on the fourth day after operation. None had hypocalcaemia on the day of surgery. Eight patients who were biochemically normocalcaemic developed hypocalcaemic symptoms.

Preoperative plasma calcium concentration correlated significantly with the weight of the resected diseased parathyroid glands but the correlation was weak ($P<0·01$, $r=0·37$). There was no significant correlation between the percentage decrease in calcium and the weight of resected glands.

There was no significant decline in the plasma calcium level on the evening after surgery but the concentration was significantly lower on the first and second days after operation in patients who required calcium supplements ($P<0·05$, *Fig. 1*). Mean(s.e.m.) percentage decrease in plasma calcium on the night of surgery compared with values before operation was greater in the calcium-supplemented group but this did not reach statistical

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Table 1 Characteristics of patients after curative parathyroidectomy

	All patients ($n = 64$)	No calcium supplements ($n = 44$)	Calcium-supplemented group ($n = 20$)
Median (interquartile range) age (years)	63 (22·5)	63 (19)	62 (30)
Histology (no.)			
Adenoma	54	37	17
Hyperplasia	8	5	3
Carcinoma	2	2	0
Weight of parathyroid Glands (g)	1·76(0·3)	1·59(0·3)	2·13(0·7)
Preoperative calcium (mmol/l)	2·91(0·03)	2·94(0·04)	2·86(0·05)
Preoperative albumin (g/l)	41·8(0·5)	41·7(0·6)	42·0(1·1)

Values are mean(s.e.m.)

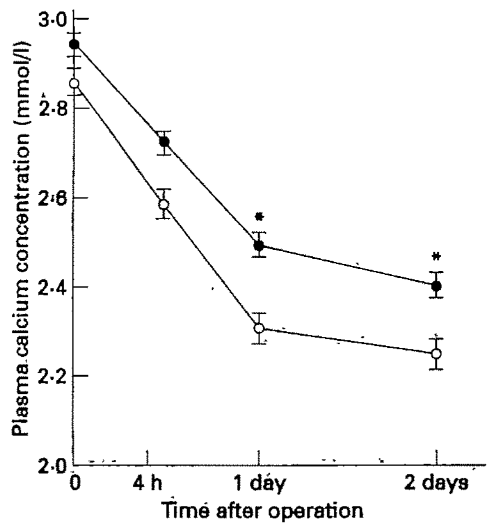

Fig. 1 Preoperative and postoperative plasma calcium levels in patients who required calcium supplements for hypocalcaemic symptoms (○) and those who did not require calcium supplements (●). Values are mean(s.e.m.). $^*P < 0{\cdot}05$ (Student's t test)

significance (9·7(1·0) *versus* 7·5(0·7) per cent, $P = 0{\cdot}06$). By the morning after operation, mean(s.e.m.) percentage reduction in calcium from preoperative values was significantly greater in the calcium-supplemented group (18·2(1·2) *versus* 14·8(0·9) per cent, $P < 0{\cdot}01$).

In the subgroup of patients who had reoperation and subtotal parathyroidectomy, percentage decrease in the plasma calcium levels on the evening after surgery was significantly higher in the calcium-supplemented group (12·8(1·3) *versus* 5·6(0·9) per cent, $P < 0{\cdot}005$, *Fig. 2*). In patients who had 1½ glands resected for adenomatous pathology, mean(s.e.m.) percentage reduction was not significantly different between the two groups (8·3(1·1) *versus* 7·8(0·8) per cent, $P = 0{\cdot}7$). There was no significant difference in the weight of resected parathyroid glands between the two groups ($P = 0{\cdot}5$) or between levels before operation of alkaline phosphatase or plasma phosphate (data not shown).

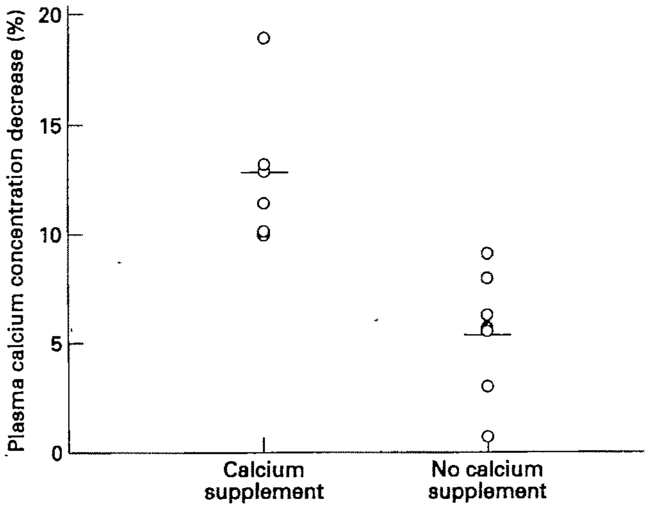

Fig. 2 Percentage decrease in plasma calcium levels in patients who required reoperation and subtotal parathyroidectomy. Bars are means. The greater decrease in plasma calcium levels in patients receiving calcium supplements is significant ($P < 0{\cdot}001$, Student's t test)

Discussion

The more aggressive the operative strategy in parathyroidectomy, the more likely the development of hypocalcaemia[1,4,5].

Curative parathyroidectomy is followed by a rapid decline in plasma parathyroid hormone levels in the immediate postoperative period[6–8]. The decrease in plasma calcium is much slower, but the rate of decline is greatest in the first 12–24 h after resection[6,7], reaching a nadir after 24 h. This possibly explains why hypocalcaemic symptoms usually occur after 24 h[9]. In this study no patient had symptoms on the day of surgery and 45 per cent were affected on the first day after operation. Recovery of plasma parathyroid hormone level occurs within 24 h after operation[6,7]. Excessive removal of parathyroid glands, parathyroid injury, or maintained suppression of parathyroid hormone may delay recovery of the remaining glands and explain the continued reduction in calcium. The rate of decline in plasma calcium level may be more important than the absolute concentration in producing symptoms[10].

Although the percentage decrease in plasma calcium level was greater in patients who required calcium supplements, the serum calcium concentration on the evening after surgery was of little use in predicting the onset of hypocalcaemia. In the subgroup of patients who had repeat operations or subtotal parathyroidectomy, however, the percentage reduction in calcium level was significantly higher (12·8 *versus* 5·6 per cent, $P < 0{\cdot}005$) and a decline of 10 per cent or more in the calcium level on the evening of surgery was consistently followed by hypocalcaemic symptoms. This higher incidence of hypocalcaemia in those undergoing reoperation or extensive exploration has been reported by others[1,4,5,11]. The drop in postoperative plasma calcium was greatest in those having a more aggressive biopsy[5]. The number of patients in the subgroup in this study was small but these findings deserve further evaluation and confirmation.

Previous studies of ionized and total calcium level showed little variation between the two and changes in the postoperative period were parallel[12–14]. Only two patients had hypoalbuminaemia, one in each group, and no patient had severe medical illness. All operations were carried out with minimal blood loss.

The biochemical threshold at which hypocalcaemic symptoms developed was variable and unpredictable, and 40 per cent of patients were normocalcaemic at the time of symptom onset. The mechanism of this is unclear but it may be caused by neuromuscular adjustment to chronic hypercalcaemia and a lowering of the threshold for hypocalcaemic symptoms.

There is considerable controversy regarding the relation between the calcium level before operation and weight of abnormal parathyroid glands[3,4,8,15,16]. A strong correlation would help determine whether the volume of gland resected was appropriate for the preoperative calcium level. The correlation was weak in this study as in others[8,15,16]. Disturbance of cytoplasmic calcium, rather than increased glandular mass, contributes to hypercalcaemia in hyperparathyroidism due to adenoma or hyperplasia[16].

Zamboni and Folse[3] reported a significantly higher incidence of hypocalcaemia in patients who had more than 2 g of parathyroid gland resected, and suggested that a large adenoma might have a suppressing effect on the remaining glands. Brasier & Nussbaum[2] found that the weight and volume of resected glands were significantly greater in patients who had hungry bone syndrome after parathyroidectomy, but the weight and volume were, however, smaller in the hypocalcaemic group. The weight of resected gland is probably not important but rather the function of the remaining glands. No significant difference in the weight of the resected glands, no correlation between the decrease in calcium level and weight of resected gland, and no difference in markers of bone disease were observed in this study.

Plasma calcium level on the evening after parathyroidectomy is of little value in postoperative management and does not help predict the onset of subsequent hypocalcaemia or symptoms. In high-risk groups (reoperation or where extensive exploration is required), however, it may be a valuable predictor of the development of hypocalcaemic symptoms.

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Laparotomy for abdominal sepsis in the critically ill

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Among 125 patients admitted to an intensive care unit (ICU) with severe abdominal sepsis over a 3-year period, further laparotomy was required in 60 (48 per cent). The median age of these 60 patients was 67 (range 22–88) years and their admission APACHE (Acute Physiology and Chronic Health Evaluation) II score was 24 (range 7–40); 25 patients (42 per cent) survived to leave the ICU but only 19 (32 per cent) survived to leave hospital. These patients underwent 95 (median 1; range 1–6) operations after admission to the ICU and survival fell with increasing number of operations in the ICU ($P = 0{\cdot}01$). A total of 81 operations (85 per cent) were therapeutic in that pus was drained or dead tissue removed, and 41 operations (43 per cent) resulted in improvement in the patient's condition within 48 h of surgery. Only nine per cent of patients not improved by their first operation in the ICU survived ($P < 0{\cdot}0001$). The source of sepsis was eradicated from the abdomen in 37 patients (62 per cent); this was a prerequisite for survival but was achieved less frequently with increasing number of operations ($P < 0{\cdot}002$). When operations were delayed until the diagnosis was clear, the need for subsequent procedures was significantly increased ($P < 0{\cdot}05$). Multiple operations for patients with abdominal sepsis in the ICU were associated with diminishing returns and alternative surgical strategies merit active consideration.

The decision to operate, sometimes repeatedly, on patients with severe abdominal sepsis in the intensive care unit (ICU) is one that many surgeons find difficult. Although severe abdominal sepsis is the most frequent reason for admission of a surgical patient to the ICU, the experience gained by an individual surgeon will be relatively limited[1,2]. Patients with severe abdominal sepsis form a disparate group and clear management guidelines for the individual patient do not exist. These patients may be young and often have 'benign' pathology so that, despite their critical illness, a successful outcome would otherwise be anticipated.

The principle of eradicating sepsis from within the abdomen is long established but the methods of achieving it and of diagnosing recurrent or continuing sepsis continue to excite comment, most notably from Germany, South Africa and the USA[3–9]. There have been few British data regarding such patients[10,11], which is surprising in view of the difficulties which they present and the effort and resources which their treatment requires. A hospital mortality rate of 63 per cent was recently reported in British patients with abdominal sepsis who required treatment in an ICU[12], and this appears worse than the results reported in series from other developed countries where aggressive surgical approaches are widely pursued[6,8]. The aim of the present study was to define current surgical practice regarding further operation for patients with severe abdominal sepsis, to determine the outcome of this surgery and consider whether alternative approaches should be adopted.

Patients and methods

Between February 1990 and June 1993, 125 patients with confirmed abdominal sepsis were treated in the ICU of the Western General Hospital, Edinburgh. The diagnosis was confirmed by laparotomy in 119 patients, by clinical and microbiological indices in five and at post-mortem examination in the remaining one. Twelve consultant surgeons were involved with treatment at the Western General Hospital but 47 patients (38 per cent) were transferred after initial hospital treatment elsewhere. Some 60 of these 125 patients underwent laparotomy while in the ICU and their management forms the basis of this report. The outcome of the entire group ($n = 125$) has previously been reported[12].

A single author reviewed the casenotes, intensive-care charts and operation notes, and extracted a range of patient details[12]. Thirty-two patients (53 per cent) had undergone emergency surgery before admission (median 1; range 1–3 operations) and, in 14 patients, an initial elective procedure had been undertaken. Nineteen patients (32 per cent) had not undergone recent surgery. The pathological processes necessitating further surgery are shown in *Table 1*. A number of points specific to the surgical treatment were identified and definitions of type of operation performed and outcome from surgery are shown in *Table 2*. Operations were reviewed to determine whether they had been 'therapeutic' and whether or not the patient's clinical condition subsequently improved. The success or otherwise of clearing the source of sepsis from the abdomen together with any significant secondary loculi was recorded. Finally, operations performed in the ICU were broken down into three classes for comparison: 'diagnostic' ($n = 29$, 31 per cent), 'planned second look' ($n = 22$, 23 per cent) and 'treatment' ($n = 44$, 46 per cent) procedures.

During the period of study, laparotomy was considered in a further four patients but these patients either succumbed before surgery could be undertaken or laparotomy was judged inappropriate on account of severe chronic disease.

Table 1 Pathological process requiring surgery for abdominal sepsis following admission to the intensive care unit

Pathological process	*n*
Leaking duodenal stump/duodenal ulcer repair	3
Leaking ileocolic or colocolic anastomosis	10
Other postoperative anastomotic leak	6
Perforated colon	12
Perforated duodenum	5
Perforated small bowel (hernia/trauma)	2
Perforated bile duct	1
Ischaemic bowel	8
Pancreatitis	4
Cholecystitis	3
Colonic obstruction/volvulus	3
Other	3

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Table 2 Definitions of terms used

Term	Definition
Therapeutic operation	Pus drained or ischaemic tissue excised
Clinical improvement	Recorded in the patient's progress notes or evident from improvement in vital organ function 24–48 h after surgery
Clearance of sepsis	Eradication from the abdomen of the source of sepsis and any secondary loculi
Operation class	
Diagnostic	Performed to investigate clinical deterioration (e.g. increased inotrope requirement)
Second look	Planned at previous operation
Treatment	To treat a defined surgical condition (e.g. drain identified abscess)

Statistical methods

Values are shown as median (range) or mean(s.d.) as specified. Statistical analysis was undertaken using a computer package (EpiInfo 5·01b, Centres for Disease Control, Atlanta, Georgia, USA). χ^2 test (with Yates' correction) and Fisher's exact test were used to compare proportions as dictated by sample size. Group values were compared with the Kruskal–Wallis test and the Mantel–Haenszel summary χ^2 test for linear trend. Statistical significance was set at $P < 0{\cdot}05$.

Results

As shown in *Fig. 1*, 95 laparotomies were performed on 60 patients during treatment in the ICU (median 1; range 1–6). Twenty-five patients (42 per cent) survived to leave the ICU but only 19 (32 per cent) survived to leave hospital. The median age of these 60 patients was 67 (range 22–88) years. Survivors (median age 61; range 43–78 years) were younger than non-survivors (median age 70; range 41–88 years; $P = 0{\cdot}004$, Kruskal–Wallis test). Of the 27 (45 per cent) female patients, only five (19 per cent) survived, while 14 of the 33 male patients (42 per cent) survived ($\chi^2 = 3{\cdot}86$, $P < 0{\cdot}05$). The admission APACHE (Acute Physiology and Chronic Health Evaluation) II score ranged from 7 to 40 (median 24) and was lower in survivors (median 21; range 7–38) than non-survivors (median 25; range 10–40, $P = 0{\cdot}07$), although not significantly. Median Acute Physiology Score was 14 (range 2–30). Twenty-three patients (40 per cent) scored chronic health evaluation points on APACHE II scoring but this did not occur significantly more often among non-survivors. The likelihood of survival deteriorated with increasing number of operations in the ICU ($P = 0{\cdot}01$, Mantel–Haenszel extended χ^2 test for linear trend) (*Fig. 1*). Age, admission APACHE II score and coexisting morbidity were not significantly different when patients requiring different numbers of operations after admission to the ICU were compared. Localized sepsis was associated with a better outcome than generalized peritonitis for all operations in the ICU and also for the first procedure alone ($P = 0{\cdot}002$; *Fig. 2*).

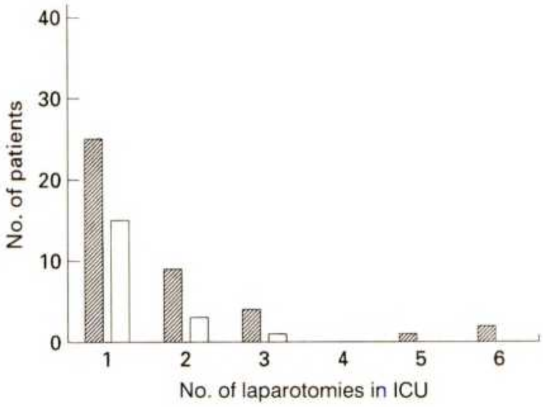

Fig. 1 Number of patients requiring different numbers of operations after admission to the intensive care unit (ICU). □, Survivors and ▨, non-survivors

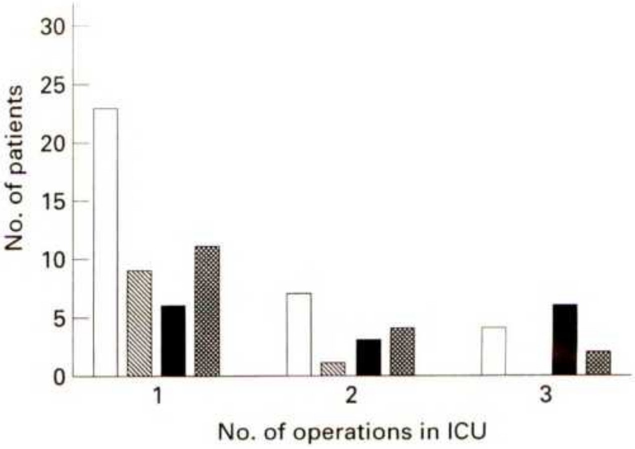

Fig. 2 Comparison between patients with localized and generalized sepsis at each operation and ultimate survival. Patients with localized sepsis had a better outcome overall ($P = 0{\cdot}002$, Mantel–Haenszel summary test) and during the first procedure alone ($P = 0{\cdot}03$, Fisher's exact test). ICU, intensive care unit; ▦, localized (alive); ■, localized (dead); ▨, generalized (alive); □, generalized (dead)

Therapeutic operations

Overall, 81 operations (85 per cent) were therapeutic (i.e. resulted in drainage of pus or removal of dead tissue) and this remained virtually constant with number of operations in the ICU (*Fig. 3*). However, the likelihood that therapeutic procedures resulted in sepsis clearance fell with increasing number of operations in the ICU ($\chi^2 = 4{\cdot}41$, $P = 0{\cdot}036$).

Clinical benefit of surgery

A total of 41 laparotomies (43 per cent) resulted in clinical improvement within 24–48 h (*Fig. 3*). Patients not improved by operation had little chance of surviving. Twenty-one of 26 patients improved by their first operation ultimately left the ICU alive, whereas only three of 33 patients who were 'not improved' survived ($P < 0{\cdot}0001$, χ^2 test). Two of these patients had subsequent operations which resulted in improvement while one was found to have acute pancreatitis.

Clearance of sepsis

The septic focus was cleared from the abdomen in 37 patients (62 per cent) and, of these, 23 (62 per cent) survived. Although two patients with continuing pancreatobiliary sepsis were sufficiently improved to be discharged to the ward, they succumbed to the effects of age and recurrent sepsis. No patient, therefore, survived to leave hospital without undergoing surgical clearance of sepsis ($P<0·0001$, Kruskal–Wallis test). The mean(s.d.) admission APACHE II score showed no significant difference between those in whom sepsis was cleared (21·8(8·3)) and those in whom it was not (24·9(7·5), $P=0·11$). Similarly, the frequency of chronic health evaluation points was not significantly different (9 of 22 *versus* 14 of 36). Clearance of sepsis did not differ between the sexes in that it was cleared in 11 of 27 female patients and 12 of 33 male patients.

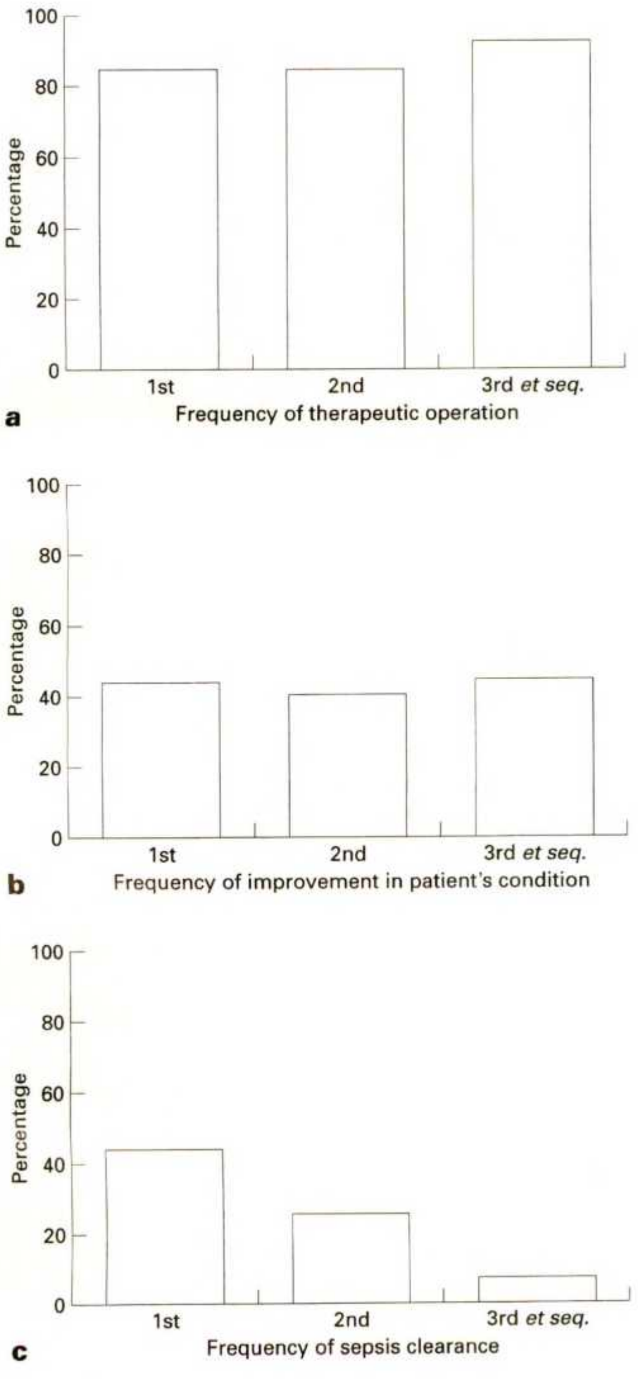

Fig. 3 The frequency of **a** therapeutic operation, **b** improvement in the patient's condition and **c** eradication of abdominal sepsis by surgery are shown for the first operation after admission to the intensive care unit ($n=60$), the second operation ($n=20$) and the third and subsequent operations ($n=15$). Surgery was commonly and consistently therapeutic (drained pus or removed dead tissue), whereas clinical improvement occurred consistently but about half as often. In contrast, the likelihood of sepsis being eradicated became significantly less frequent during subsequent operations

Of the 60 patients, sepsis was cleared in 37. In five who underwent laparotomy (of whom four survived), sepsis clearance was confirmed without the need for further definitive surgery — the procedure was non-therapeutic. Sepsis was cleared at the first ICU operation in 26 patients of whom 16 (62 per cent) survived, at the second ICU operation in five patients of whom two (40 per cent) survived and at the third ICU operation in one patient (who survived). Sepsis was therefore cleared at 26 of 60 (43 per cent) first operations, five of 20 (25 per cent) second operations and one of 15 (7 per cent) subsequent operations (*Fig. 3*). The likelihood of sepsis being cleared therefore diminished significantly with the need for further operation ($P<0·002$, χ^2 test; *Fig. 3*), but the likelihood of survival following sepsis clearance did not diminish significantly.

Operation class

Of the 95 operations performed following admission to the ICU, 29 (31 per cent) were 'diagnostic', 22 (23 per cent) were a 'planned second look' procedure and 44 (46 per cent) were 'treatment' procedures (*Table 1*). Some patients having more than one operation in the ICU underwent operations of different classes and analysis of survival in these cases is difficult unless the first operation only is taken as being type-classifying. The lower survival rate associated with 'diagnostic' procedures was not significantly different ($P=0·11$, χ^2 test) nor was 'planned second look' laparotomy associated with a better outcome when compared with other classes of operation (*Table 2*). None of the differences in the admission APACHE II or chronic health evaluation points between classes were significant.

Overall, there was no difference between operation types in their ability to clear sepsis, nor in the frequency with which pus was drained or ischaemic tissue excised (*Table 3*). 'Treatment' operations resulted in clinical improvement in 25 of 43 cases (58 per cent), more often than 'diagnostic' (nine of 29 (31 per cent), $P<0·04$) or 'planned second look' (five of 20 (25 per cent), $P<0·03$) procedures, but these differences were not seen when the therapeutic operations from each class were compared (*Table 4*). Further surgery was more commonly required

Table 3 Value and outcome of first operation following admission to the intensive care unit by operation class ($n=60$)

Operation class	n	Therapeutic	Survived	APACHE II	CHE
Diagnostic	23	16	6 (26%)	25·2 (8·9)	11 of 23
Planned second look	7	6	3 (43%)	17·4 (7·1)	1 of 7
Treatment	30	30	15 (50%)	22·4 (7·0)	11 of 28

APACHE, Acute Physiology and Chronic Health Evaluation; CHE, chronic health evaluation

Table 4 Clearance of sepsis and number of therapeutic procedures by operation class

Class	n	Sepsis cleared	Therapeutic
Diagnostic	29	10 (34)	20 (69)
Second look	22	5 (23)	16 (73)
Treatment	44	17 (39)	44 (100)

Values in parentheses are percentages

following a 'treatment' procedure (13, 43 per cent) than after 'planned second look' (1, 14 per cent) or 'diagnostic' (4, 18 per cent) operations ($P < 0.05$ treatment *versus* others combined, $\chi^2 = 3.89$, Yates' correction).

Discussion

The data presented in this study confirm that adequate surgical treatment is a prerequisite for survival among critically ill patients with abdominal sepsis[5]. The mortality rate in these patients is high (50–75 per cent)[11,13–16] and increases as more operations are required. In fact, only one patient survived to leave hospital after more than two operations during the time spent in the ICU. Other patient related factors governing outcome include the admission APACHE II score[4] and age[4,5,17]. In the present series only two patients of 24 who were aged 70 or over survived; both had simple pathology and required a single operation. The severity and type of abdominal sepsis and the patient's response to it were also influential. Upper gastrointestinal sepsis is associated with a worse outcome than sepsis of colorectal origin[12] probably because of the comparative difficulty of definitive secondary surgery in the former. Predictably, localized sepsis had a better prognosis than generalized peritonitis at each stage; localization must reflect the patient's immune response as well as primarily disease related local factors[18].

In 1926 Kirschner[19] stated that 'the opinion seems to be gaining ground that in evacuating the pus in peritonitis, the advantages outweigh the disadvantages' and this remains true. Eradicating the source of sepsis is clearly vital; none of the present patients who required laparotomy survived unless this was achieved. In a retrospective analysis there may be a tendency for this to be a self-fulfilling prophecy, but the international literature describes sepsis clearance as an 'established principle'[2,3,6–8,12,20,21] and the authors' data support this. The window of surgical opportunity is not wide[4,5,13] and the chance of clearing the sepsis decreases rapidly as more operations are required. In their prospective study of 111 patients, Billing *et al.*[4] showed that the mortality rate was only 14 per cent among patients in whom sepsis was eradicated at the first operation, but was 64 per cent when two or more operations were needed. While clearance of sepsis offers the only chance of survival in these patients, these data suggest that, even when sepsis is cleared, survival is less common after second or subsequent procedures[5]. The role that operations themselves play in the progressive immune dysfunction found in patients with severe abdominal sepsis is not clear. The close relationship between prompt improvement in a patient's clinical condition following surgery and outcome merits comment. It is accepted that clinical improvement is a relatively soft sign but here is further evidence for the importance of intervening to break the downward spiral which otherwise characterizes the natural history of abdominal sepsis.

Although 68 per cent of patients had undergone surgery before admission to the ICU, the operations performed following admission detected significant pathology in over 80 per cent of cases. This rate did not fall with increasing number of operations and was high (69 per cent) even when laparotomy was undertaken as a diagnostic procedure. Widening the indications for operation in these patients can prevent treatable abdominal sepsis being overlooked and it has previously been proposed that a negative laparotomy rate of 30–50 per cent might be acceptable among patients with multiple organ failure (MOF)[20,22]. Only 12 of the laparotomies (13 per cent) in this series were negative.

The policy of 'laparotomy on demand', where further surgery is undertaken only when clearly indicated, is an approach which implies that surgical salvage remains possible after the patient's own defence mechanisms have been overwhelmed. This position is difficult to support: performing a further laparotomy to drain pus in patients with established MOF results in only 24 per cent surviving[6,13]. The difficulty of diagnosing recurrent sepsis in patients with MOF often results in important delay[16] and, in one study of 11 patients undergoing laparotomy in the presence of MOF, pus was found in six (of whom two survived) despite negative radiological examination[17]. Alternative surgical strategies have been advocated, including routine planned second look laparotomy and laparostomy. Survival rates of 60–92 per cent are reported following laparostomy performed selectively in expert centres[9,23,24] and impressive survival figures (70–80 per cent) have been claimed by those employing a policy of 'planned relaparotomy'[4–8,11]. This policy involves the abdomen being reopened every 12–48 h until clean[3,8,25] and the formation of abscesses and other complications is said to be prevented or aborted[4,6,8], thus removing the need for a difficult laparotomy 'on demand' at 7–10 days after the initial procedure[2,20].

The classification of operation types in the present series was made retrospectively but some conclusions can still be drawn. 'Diagnostic' procedures were associated with a poorer survival but the indications for surgery were weaker and some were final attempts to find a treatable focus of infection. Nevertheless, pus or ischaemic tissue was frequently found in 'diagnostic' and 'second look' laparotomies, suggesting that more 'second look' laparotomies should be performed. It can be argued that 'planned second look' procedures are carried out slightly earlier[4,6] in the evolution of the abdominal septic process than a 'diagnostic' or 'treatment' procedure. 'Treatment' operations were associated with a higher rate of subsequent operations, perhaps suggesting that waiting for a clear indication for surgery results in more surgical complications.

No prospective studies have compared 'on demand' surgery with planned relaparotomy, although the latter has many advocates[3–8]. However, one study has compared the results of two groups of surgeons within the same hospital who simultaneously followed different policies[9]. No difference in outcome was found between the patients treated by 'planned second look' laparotomy and those treated by 'on demand' surgery, but the rate of further surgery in the 'on demand' group was higher than might be expected. The results of planned relaparotomy reported by Teichmann *et al.*[6] are particularly noteworthy in that their patients appear to have been as old and sick as those in this study. A 77 per cent survival rate was achieved in patients with a mean age of 63 years, mean admission APACHE II score of 23, of whom 51 had peritonitis for at least 48 h before entry to the programme of planned relaparotomy.

Surgery is no panacea: those with experience of both laparostomy and planned relaparotomy accept that mechanical abdominal cleansing can offer only a finite benefit to these patients[7], and the poor outcome from one study of laparostomy has been attributed to over-generous indications[10]. Attempts have been made to focus aggressive treatments on those predicted not to survive with conventional management and the consensus indicates that only 10–20 per cent of all patients with diffuse secondary peritonitis benefit from aggressive techniques[6,8,26]. These include patients aged over 70 with anastomoses which have leaked, those in whom the source of sepsis is not eradicated, those with MOF, and patients in whom there is delay (more than 48 h) in diagnosing diffuse peritonitis. This would have included at least 66 per cent (83 of 125) of the critically ill patients with abdominal sepsis treated in the ICU during the period of this study.

It is clear that the surgical treatment of patients with sepsis in the ICU must be adequate and timely. The present high mortality rate undoubtedly reflects the age and degree of physiological derangement of many of these patients but the approach of laparotomy 'on demand' possesses intrinsic shortfalls and aggressive surgical regimens may offer survival advantage. A prospective trial of planned laparotomy among British patients with severe abdominal sepsis has much to recommend it.

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Laparoscopic mobilization of the stomach for oesophageal replacement

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Nine patients of mean(s.d.) age 61(8) years underwent oesophagogastrectomy with laparoscopic gastric mobilization and abdominal lymphadenectomy for oesophageal cancer. Moderate to severe airway obstruction was present in all patients, in whom the mean(s.d.) value of forced expiratory flow rate at 1 s was 65(17) (range 35–85) per cent of the predicted value. Six patients had an abdominal laparoscopic approach combined with a right open thoracotomy; the other three had a laparoscopic abdominal and transhiatal approach combined with a left cervicotomy. No patient required conversion to open laparotomy. All had an uneventful postoperative course with extubation occurring at the end of the surgical procedure ($n = 2$) or on day 1 after operation ($n = 7$). Mean(s.d.) duration of hospitalization was 10·3(3·1) (range 8–18) days. The laparoscopic approach for gastric mobilization and abdominal lymphadenectomy is safe and can be used in patients with impaired pulmonary function.

Postoperative pulmonary complications remain the main cause of morbidity and mortality after oesophagectomy[1,2]. Oesophageal resection with gastroplasty includes an abdominal step for gastric mobilization and coeliac lymphadenectomy, whatever the location and stage of the tumour. It has been demonstrated that the laparoscopic approach preserves pulmonary function in upper abdominal surgery[3–5]. To improve the postoperative pulmonary course after oesophagectomy, the laparoscopic approach for gastric mobilization in oesophageal replacement was evaluated prospectively.

Patients and methods

Between August and December 1994, nine patients (seven men and two women) with a mean(s.d.) age of 61(8) (range 50–79) years with oesophageal cancer underwent oesophagogastrectomy with laparoscopic gastric mobilization. The indication for oesophageal resection was squamous cell carcinoma located in the upper third ($n = 1$), middle third ($n = 1$) or lower third ($n = 7$). No patient had coeliac lymph node enlargement on preoperative computed tomography. Moderate to severe airway obstruction was present in all patients; mean(s.d.) forced expiratory flow rate at 1 s (FEV-1) was 65(17) (range 35–85) per cent of the predicted value; the lowest value of FEV-1 was 860 ml/s. Six patients underwent an abdominal laparoscopic approach combined with a right thoracotomy (modification of the Ivor–Lewis procedure) and three patients with worse pulmonary function had a laparoscopic abdominal and transhiatal approach combined with a left cervicotomy (modification of transhiatal oesophagectomy).

Operative technique

Abdominal laparoscopic approach combined with right thoracotomy. The procedure began with the laparoscopic phase. Six cannulas were inserted (*Fig. 1*). First, the diaphragmatic hiatus was defined after division of the lesser omentum. The abdominal oesophagus was controlled by a tape and the anterior part of the hiatus was divided by electrocoagulation. Adequate mobilization of the stomach consisted of an extensive Kocherization of the duodenum, division of the greater omentum with selective ligation by endoclips of the omental vessels, the left gastroepiploic vessels and the vasa brevia. The right gastroepiploic vessels were carefully preserved. With anterior retraction of the stomach, the left gastric vessels were defined and divided between clips and ligatures, using an intracorporeal knot tying technique, close to the coeliac axis (*Fig. 2*). Left gastric, splenic and coeliac lymphadenectomy was performed. Pyloroplasty was not performed. The right hemithorax was opened through the fifth intercostal space. Oesophagectomy combined with a posterior mediastinal lymphadenectomy was performed. The stomach was carefully pulled up into the chest and the lesser curve was resected with a linear stapler (GIA;

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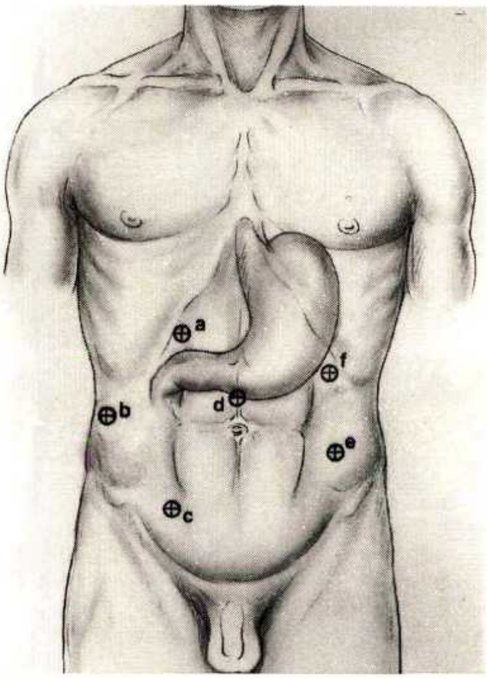

Fig. 1 Position of the cannulas for laparoscopic gastric mobilization: **a**, retractor of the left liver lobe (5 mm); **b**, grasping forceps for retraction of the stomach (5 mm); **c**, grasping forceps for retraction of the greater omentum (5 mm); **d**, 0° laparoscope (10 mm); **e**, grasping forceps for traction of the encircled oesophagus and laparoscope during division of the vasa brevia (10 mm); **f**, electrosurgical scissors, clip applicator (10 mm) or stapler in the transhiatal procedure (12 mm)

Auto Suture, Lyon-Bron, France) through the thoracic approach. Standard intrathoracic oesophagogastric anastomosis was performed with a circular stapler (PCEEA; Auto Suture).

Transhiatal laparoscopic oesophagectomy. The number and location of the abdominal cannulas were similar to those of the previous procedure (*Fig. 1*). During the laparoscopic phase, after gastric mobilization, the lower and mid-oesophagus was freed transhiatally under videoscopic control. The vagus nerves were divided between endoclips at the inferior edge of the main stem bronchi. The oesophagogastric junction was then divided with a stapler (Endo GIA; Auto Suture) to exteriorize the stomach through a minilaparotomy located in the right upper quadrant just in front of the pylorus. Resection of the lesser curve and pyloroplasty were performed extracorporeally. After oesophageal resection via a left cervical approach, the gastric tube was reintroduced into the abdomen and pulled upward to the cervicotomy where a standard oesophagogastric handsewn anastomosis was performed.

Results

There were no operative deaths. Peroperative thoracic drainage for pneumothorax was necessary in one patient. Patients are listed in *Table 1*. The mean(s.d.) time for the laparoscopic step was 210(25) (range 170–250) min. The mean(s.d.) operating time was 511(87) (range 360–610) min. The mean(s.d.) duration of the combined laparoscopic–right chest approach was 504(62) min and that of the laparoscopic transhiatal procedure was 522(142) min (not significant). At the end of the procedure, the mean(s.d.) body temperature was 34·3(0·7) (range 33·5–35·4) °C. All patients had an uneventful postoperative course. Postoperative extubation occurred at the end of the surgical procedure in two patients and on day 1 in seven. The mean(s.d) reduction of forced vital capacity at day 8 after operation was 15(11) (range +30 to −5) per cent of the preoperative value. The mean(s.d.) duration of hospitalization was 10·3(3·1) (range 8–18) days. There were no patients with delayed gastric emptying. The mean(s.d.) number of abdominal lymph nodes found in the resected specimen was 8·1(2·5) (range 5–13).

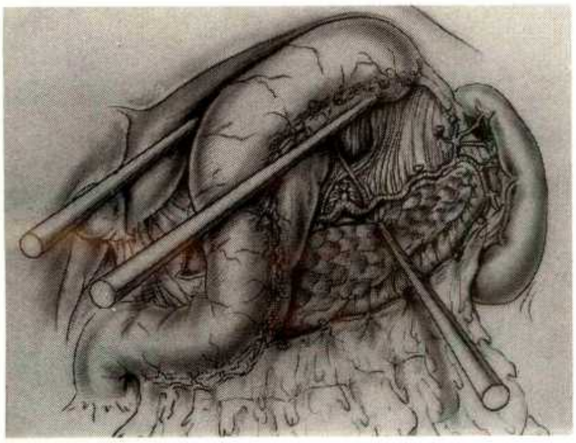

Fig. 2 Laparoscopic coeliac lymphadenectomy

Table 1 Operative data

Patients no.*	Procedure	Duration of laparoscopic phase (min)	Body temperature (°C)†	Extubation (days after operation)
1	TH	250	34·8	1
2	L	240	33·7	1
3	TH	215	34·5	1
4	L	205	33·5	0
5	L	210	35·4	1
6	L	215	35·2	1
7	L	170	33·8	1
8	TH	205	34·2	1
9	L	180	34·1	0

*Patients are listed in chronological order. †At the end of the procedure. L, laparoscopic Lewis procedure; TH, laparoscopic transhiatal procedure

Discussion

The ideal approach for oesophagectomy with oesophageal replacement has not yet been defined. Postoperative pulmonary dysfunction and pulmonary infections remain a considerable problem, to which the combined thoraco-abdominal approach is one of the largest contributing factors[6]. In fact, thoracotomy in oesophageal surgery is more hazardous than in other indications[7] and additional laparotomy leads to a greater disturbance of pulmonary function and increased pain[6]. Oesophagectomy without thoracotomy, achieved either by the transhiatal procedure or by thoracoscopic oesophagectomy, has been proposed to improve the postoperative pulmonary course[8]. However, the transhiatal approach precludes thoracic lymph node dissection and it is not clear whether it reduces the incidence of postoperative pulmonary complications[9]. Thoracoscopic oesophagectomy has a poor postoperative pulmonary course, as observed in seven patients, in the authors' experience, and in recent series[10,11]. To improve the functional tolerance of oesophageal surgery, a laparoscopic approach was used for gastric mobilization and abdominal lymphadenectomy since laparoscopy reduces postoperative pain and improves early postoperative pulmonary function compared with upper laparotomy[7].

The laparoscopic approach was derived from laparoscopic antireflux surgery: the position of the cannulas was similar with an additional cannula in the left flank for the division of the vasa brevia. The procedure was feasible in all cases. However, this result should be viewed with caution since none of the present patients was obese. Gastric mobilization and abdominal lymphadenectomy were conducted in the same fashion as for open laparotomy, and a similar number of abdominal lymph nodes was found in the specimen.

No port site metastases were observed after a short follow-up. This serious complication has impaired the results of laparoscopic surgery for malignancy[12]. However, the risk in this procedure is probably lower than encountered in surgery for abdominal tumours because of the absence of tumour mobilization at this phase. The present results suggest that the main advantage of the laparoscopic approach is good tolerance as all patients made a remarkably fast postoperative recovery.

These preliminary results support the hypothesis that this new approach may be useful in patients with impaired pulmonary function. However, it is time consuming and exposes the patient to hypothermia at the end of the procedure, which led to delayed extubation in seven of nine patients in the present series. Although it did not impair the postoperative course, hypothermia should be actively prevented during the procedure.

Gastric outlet obstruction was not encountered in this series but occurs in 15 per cent of patients after an open Ivor–Lewis procedure without pyloroplasty[13]. The proportion of symptomatic patients who require reoperation is small and endoscopic balloon dilatation is now an attractive alternative to surgery. For these reasons, it was decided not to perform a pyloroplasty in the modified Ivor–Lewis procedure.

The authors believe that laparoscopy is now a useful tool in the surgical armament for oesophageal cancer but further investigations are needed to determine more precisely the benefit of this technique on the postoperative pulmonary course and long-term survival.

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Fc-receptor function after human splenic autotransplantation

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Mononuclear phagocytic function was studied using the Fc-receptor test in 24 patients who underwent splenectomy, ten of whom underwent splenic autotransplantation. All patients undergoing autotransplantation had mononuclear phagocyte system (MPS) activity at the transplantation sites. In eight of the 14 patients who did not undergo autotransplantation there was also scintigraphic MPS activity indicative of ectopic splenic tissue. Although the Fc-receptor test showed delayed and monoexponential blood clearance in all patients after splenectomy, there were no significant differences between the patient groups. Autotransplantation of small amounts of splenic tissue after splenectomy provides some MPS activity but is inadequate for blood clearance.

Splenectomy results in an increased risk of sepsis, the so-called overwhelming postsplenectomy infection (OPSI) syndrome, which carries a high mortality rate, especially in children[1–3]. This syndrome is likely to be caused by a defect in the immune system after splenectomy[4–6].

The mononuclear phagocyte systems (MPSs) of the liver and spleen show clear differences in opsonization requirements. Whereas phagocytosis by the liver MPS requires adequate opsonization of antigen with immunoglobulin and/or complement, the splenic MPS is able to phagocytose poorly or non-opsonized antigens. This property is unique to the spleen[7], and is particularly important in the defence against thymus-independent type 2 antigens, such as those of *Streptococcus pneumoniae*, the main cause of OPSI[8]. Animal experiments have suggested that autotransplantation of splenic tissue (AST) after splenectomy restores this particular splenic MPS function[8–10]. The result of AST in humans has been evaluated using ^{99m}Tc colloid scintigraphy[11–13] and Cr-51 anti-rhesus factor antibody coated erythrocytes[14]. However, it remains unclear whether or not AST in humans restores MPS function after splenectomy.

A method of measuring MPS function has been developed which involves the clearance of radiolabeled rhesus-positive (intact) erythrocytes coated at low density with anti-rhesus antibody in patients with systemic lupus erythematosus[15] and Wegener's granulomatosis[16]. This Fc-receptor test is considered to provide a parameter of *in vivo* splenic MPS Fc-receptor function[17–19]. Low-level opsonization of the erythrocytes provides good uptake by the splenic Fc-receptors and reduced Fc-receptor uptake in the liver.

To evaluate whether autotransplanted splenic tissue may be capable of restoration of MPS function after splenectomy, this assay was employed in patients, with and without splenic autotransplantation after splenectomy, from whom the blood clearance and 'spleen' uptake curves were analysed.

Patients and methods

Patients

Splenectomy was performed either for trauma or as part of the surgical procedure during partial gastrectomy for peptic ulcer in 24 male patients, mean age 27·3 (range 15–55) years, none of whom had malignant or autoimmune disease. During the operation a thorough examination for ectopic splenic tissue was performed. When ectopic splenic tissue was found, the patients were excluded from the study.

In ten of these patients autotransplantation was performed after splenectomy: a 5 × 5 × 5-cm piece of splenic tissue (approximately 25 g) was cut into 2–3-mm cubes and implanted in the greater omentum, fixed with a purse-string suture and marked with a silver clip. In the remaining 14 patients autotransplantation was not performed.

The project was approved by the hospital medical ethics committee and informed consent was obtained from all patients.

Test procedures

To exclude any effects of trauma and/or operation the time interval between operation and the Fc-receptor test was at least 6 months (range 0·5–2·5 years).

The Fc-receptor test has been described previously[15,16]. In brief, rhesus-positive red blood cells from a single donor were incubated with a 1 : 2 dilution of anti-rhesus (D) antiserum. Small numbers of cells were stored in 10-ml aliquots at −80°C. On the day of the clearance study the contents of one vial were labelled with ^{99m}Tc (efficiency rate greater than 90 per cent); the amount of radioactivity administered intravenously was 30 MBq. The upper abdominal region was scanned with a dual-headed gamma camera (Siemens ROTA, Des Plaines, Illinois, USA) and computer (DEC Gamma 11; Siemens) in 1-min frames over 1 h. Blood samples were taken after 0, 1, 2, 3, 5, 8, 13, 18, 23 and 30 min and then every 10 min up to 2 h. The localization of 'hot spots' on the scan was compared with abdominal radiographs, visualizing the original localization of the spleen transplants, marked with silver clips. The blood curve was examined using the compartment model[16,20], the compartments studied being blood, spleen and liver. On entry into the spleen the ^{99m}Tc-labelled and immunoglobulin (Ig)G-coated erythrocytes are trapped either temporarily or permanently[14]. The assumption is made that reversibly trapped erythrocytes re-enter the blood by first-order kinetics. Because of the low level of opsonization the reversible pool is not situated in the liver but the spleen. This model would predict a biexponential clearance from the blood of the coated and labelled erythrocytes in case of a truly reversible compartment. Without any reversible compartment the clearance will be monoexponential[20].

In this study the shape of the whole blood curve over 2 h was investigated by the least squares fitting method with both a biexponential and a monoexponential function[16,20]. The sum of the squared deviations between the measured data points and the theoretical functions in both fit procedures, the so-called χ^2 values, were used to describe the shape of the experimental curve. For a biexponential curve the χ^2 value for the fit is much smaller than for the monoexponential fit; the ratio of both χ^2 values, the so-called F value, is much less than unity. For a

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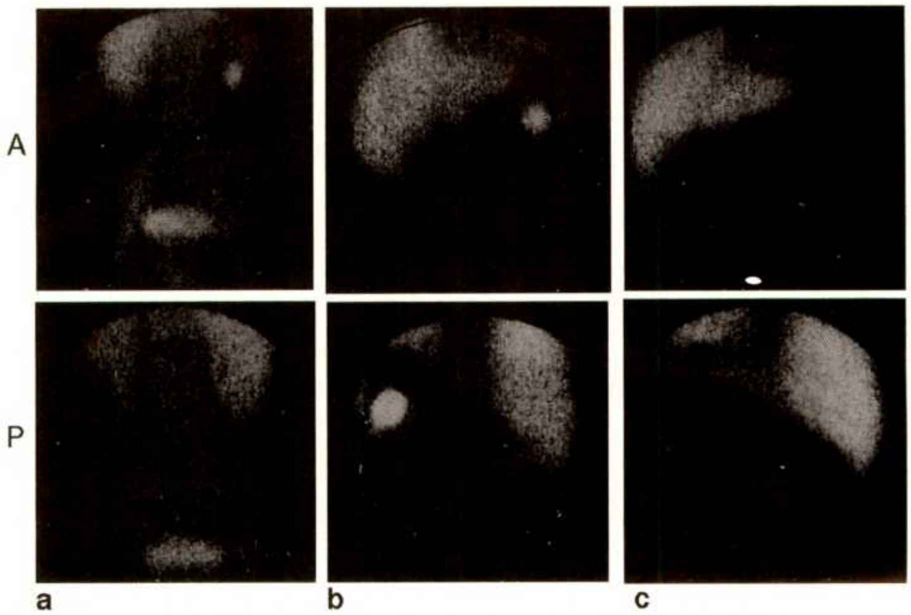

Fig. 1 Scintigrams of liver and spleen using ^{99m}Tc immunoglobulin (Ig)G-coated erythrocytes; anterior (A) and posterior (P) view. **a** After splenectomy and autotransplantation of splenic tissue; **b** after splenectomy with ectopic splenic tissue; and **c** after splenectomy without ectopic splenic tissue

monoexponential curve the χ^2 values of both fits are equal, resulting in an F value near unity[16-20].

Statistics

For statistical analysis the non-parametrical Kruskal–Wallis test was used.

Results

Scintigraphy

In all patients undergoing splenic implantation (n = ten) scintigraphy showed a hot spot at the site where the splenic tissue had been reimplanted. The spot was small in all patients, corresponding with the small amount of implanted tissue.

In eight of the 14 patients who did not have an AST procedure a hot spot was found in the upper left abdomen; this spot was considered to represent ectopic splenic tissue. In the remaining six patients no such spot was found (no splenic tissue group). Scintigraphs of the patients are shown in *Fig. 1*.

Blood clearance

The blood clearance curves of the coated and labelled erythrocytes were abnormal compared with normal subjects ($P < 0.05$). There were no significant differences between the two patient groups (*Table 1* and *Fig. 2*). The curves did not show signs of a reversible compartment and were flat, with high χ^2 values for the monoexponential fit. The F values were high in all three groups (in biexponential curves they are low), and there were no statistically significant differences between the groups (*Table 2*). The half-lives of the coated and labelled erythrocytes were very long but there were no significant differences between the two patient groups (*Table 2*).

Table 1 Percentage radioactivity of blood samples in the three patient groups

Time (min)	AST (%)	EST (%)	NST (%)
1	47(38)	53(35)	73(22)
2	87(18)	93(8)	97(4)
3	91(9)	95(6)	96(3)
5	94(9)	86(12)	90(9)
8	92(9)	86(10)	91(6)
13	90(10)	81(11)	88(6)
18	85(10)	78(12)	87(4)
23	86(10)	73(11)	87(7)
30	84(9)	73(11)	81(4)
40	80(9)	69(12)	78(7)
50	78(10)	67(10)	74(7)
60	77(9)	62(10)	70(8)
70	73(9)	62(13)	69(8)
80	69(7)	59(11)	70(7)
90	71(10)	59(14)	70(8)
100	67(9)	53(10)	67(8)
110	68(9)	53(13)	64(11)
120	68(12)	54(13)	62(9)

Values are mean(s.d.). AST, autotransplantation of splenic tissue; EST, ectopic splenic tissue; NST, no splenic tissue

Discussion

The Fc-receptor test used in this study measures blood clearance and degree of reversible splenic pooling of low density IgG-coated red cells. A prolonged half-life, and splenic trapping which is either diminished or absent has been found in patients during active phases of systemic lupus erythematosus and Wegener's granulomatosis[15,16]. These results were interpreted as a saturation of the Fc-receptors in the spleen by circulating immune complexes, i.e. as decreased functional splenic MPS activity. Such a

Table 2 Results of Fc-receptor test in patients after splenectomy

Patient no.	Half-life (min)	Monoexponential*	Biexponential*	*F*
AST				
1	152	1291	96	0·07
2	205	1043	720	0·69
3	370	1015	515	0·51
4	—	—	—	—
5	167	71	11	0·15
6	140	820	544	0·66
7	630	1584	—	1·0
8	136	428	341	0·80
9	186	462	99	0·21
10	263	2415	299	0·12
Mean(s.d.)	250(152)			0·47(0·32)
EST				
11	133	1354	793	0·59
12	374	986	772	0·78
13	111	942	364	0·39
14	178	555	356	0·64
15	187	1891	169	0·09
16	109	1137	245	0·22
17	107	1041	83	0·08
18	145	1861	247	0·13
Mean(s.d.)	168(83)			0·37(0·26)
NST				
19	310	1388	1028	0·74
20	237	356	109	0·31
21	215	739	707	0·96
22	91	1365	793	0·58
23	197	1116	563	0·50
24	351	766	760	0·99
Mean(s.d.)	234(83)			0·68(0·24)

AST, autotransplantation of splenic tissue; EST, ectopic splenic tissue; NST, no splenic tissue. Reference values[16] are: half-life, 29 (range 11–56) min; $F = 0$–$0·1$; *χ^2 test

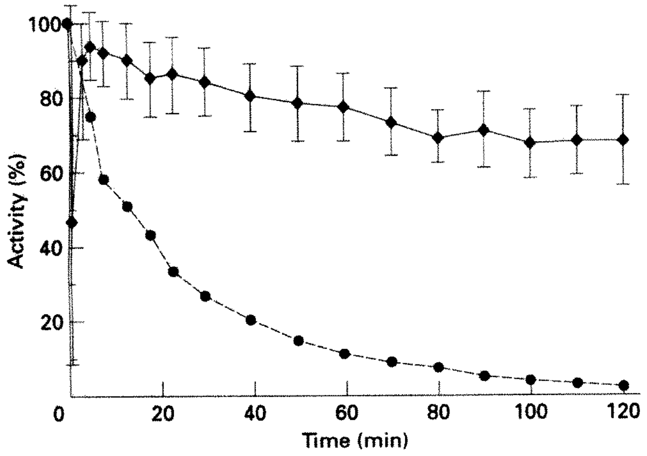

Fig. 2 Blood clearance curve (in percentage activity) of ^{99m}Tc-labelled immunoglobulin (Ig)G-coated erythrocytes. Normal pattern with biexponential shape (———) and mean curve of the autotransplanted patients (----). Mean curves of the other patient groups were not significantly different

decrease can be interpreted as functional hyposplenism, but the effects of therapy, e.g. corticosteroids, on Fc-receptor function cannot be excluded. With this in mind, in the present study the Fc-receptor test was used in patients after splenectomy and autotransplantation of splenic tissue in order to investigate the MPS function of the reimplanted tissue.

In the scintigraphy studies a hot spot was seen at the site of splenic autotransplantation suggesting the presence of functional MPS tissue. In eight patients without autotransplantation positive scintigraphy was also seen, showing either the presence of a residual accessory (or ectopic) spleen or possibly localized splenosis because all these patients had a disrupted spleen.

The blood clearance curves were not significantly different between splenectomy patients with and without autotransplantation, or with ectopic splenic tissue. The test measures reversible pooling of cells in the spleen. Scintigraphy showed that 'phagocytic tissue' with functional 'splenic' Fc-receptors was present. In normal individuals the coated erythrocytes pool in the spleen resulting in a biexponential blood clearance (*Fig. 2*, ———), but in active phases of diseases such as systemic lupus erythematosus and Wegener's granulomatosis this pooling appeared to be absent resulting in a monoexponential blood clearance (*Fig. 2*, ----) with a prolonged half-life[15,16]. In a compartmental model with a reversible pool in the spleen this indicates strongly reduced splenic MPS function resulting in 'functional hyposplenism'. The results in this study indicate that, compared with patients with systemic lupus erythematosus and Wegener's granulomatosis, functional hyposplenism with respect to overall Fc-receptor function occurs after splenectomy. In autotransplanted patients the resulting 'spleen' was small (less than 10 per cent of the normal size) and the blood supply was much lower than that of the normal spleen.

The degree of antibody coating used in the present study was chosen because of the optimal splenic uptake; a higher degree of coating may result in a better liver uptake and a shorter blood half-life[16], therefore this may not be an adequate assay of splenic MPS function. Although restoration of general MPS activity is relevant, it should be appreciated that densely Ig-coated (well opsonized) erythrocytes are not typical of the badly opsonized microbial antigens that are known to cause problems in OPSI.

In conclusion, scintigraphy with IgG-coated red cells showed a hot spot at the site of splenic implantation indicating the presence of Fc-receptor-bearing (phagocytic) cells, but the results of the analysis of the kinetics of these cells are not characteristic of adequate restoration of overall splenic Fc-receptor function. Based on the present study, autotransplantation of a small amount of splenic tissue after splenectomy cannot be considered sufficient to restore splenic MPS function, especially in relation to low-opsonized antigens. Therefore, at present medical prophylaxis is required to prevent OPSI in patients who have undergone splenectomy even when splenic autotransplantation has been performed. Further studies of MPS function after splenic autotransplantation may require procedures in which a considerable mass of well vascularized splenic tissue is transplanted in the hope that MPS function of the autotransplanted spleen will be preserved.

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Laparoscopic surgery for duodenal ulcer: first results of a multicentre study applying a personal procedure

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Between January 1991 and February 1995 data were gathered on 136 patients operated on in 14 surgical centres. All patients underwent posterior truncal vagotomy (PTV) and anterior linear gastrectomy (ALG) for chronic duodenal ulcer. Recurrence and repeated bleeding were the main indications for surgery. An antireflux technique was simultaneously carried out in 17 patients, while 13 underwent cholecystectomy. There were no peroperative complications or deaths, and the mean duration of operation was 65 (range 25–180) min. Immediate postoperative morbidity rate was 2·9 per cent, with a mean hospital stay of 3·1 (range 2–13) days. A total of 131 patients were evaluated between 6 and 33 (mean 25) months after operation. Of these, 126 (96·2 per cent) were graded as Visick I or II. Four (3·0 per cent) were Visick III, and one patient (0·8 per cent) was considered Visick IV. Gastric function studies were performed in 45 patients before and after operation, with a maximum acid output reduction of 83 per cent 3 months after the operation. Laparoscopic PTV with ALG constitutes a simple, efficient, rapid and safe method in the treatment of patients with chronic duodenal ulcer.

The efficacy of laparoscopic surgery in the treatment of chronic duodenal ulcer has been demonstrated in the short and medium term by a number of authors employing different methods. Conventional techniques have been applied using minimally invasive approaches, including transthoracic truncal vagotomy[1]; transabdominal truncal vagotomy[2], alone or in association with pneumatic dilatation of the pylorus, pyloromyotomy or pyloroplasty; truncal vagotomy and antrectomy, anterior and posterior supraselective vagotomy[3]; posterior truncal vagotomy (PTV) and supraselective anterior vagotomy[4]; PTV and anterior seromyotomy[5,6]; and PTV with anterior linear gastrectomy (ALG)[7–9].

Based on the hypothesis that gastrotomy with eversion sutures would be more effective than seromyotomy, Gómez-Ferrer *et al.*[10–12] began, in 1986, removing a fold of the anterior wall of the stomach in close proximity to the lesser curve, using a mechanical stapler. This technique was called ALG. This procedure was in turn supported by the results obtained in two experimental studies[13,14], and a recent report from Belgium confirms the value of the technique at open operation[15].

The aim of the present study was to report early results in 136 patients with chronic duodenal ulcer subjected to PTV and ALG. In this sense, the limited number of patients involved ruled out a prospective randomized study.

Patients and methods

A simple protocol was issued to all participating centres, comprising the measures described below.

A total of 136 patients (111 men) from 14 surgical centres were studied (see Appendix). Mean age was 48·1 (range 23–69) years. The mean duration of the disease was 9·5 (range 3–19) years. Associated pathology in the form of gastro-oesophageal reflux and biliary lithiasis was observed in 17 and 13 patients respectively. Sixty-five patients had suffered one or more episodes of bleeding in the past. The remainder failed to respond to or comply with medication.

Preoperative evaluation

Eighty patients underwent gastroduodenal transit evaluation. Eighty-six patients were subjected to oesophagogastroduodenal endoscopy to confirm the diagnosis of duodenal ulcer and exclude pyloric stenosis, gastric ulcer, gastro-oesophageal reflux, oesophagitis and/or hiatal hernia. All patients consulted the surgical services directly; as a result, no routine evaluation or treatment of possible *Helicobacter pylori* infection was carried out in the period 1991–1993. Possible *H. pylori* infection was evaluated by biopsy, whenever the latter was performed. H_2 blockers, omeprazole and amoxycillin were associated when *H. pylori* was apparent.

Hepatobiliopancreatic echography was performed in 35 patients, and basal acid output (BAO), maximum acid output (MAO) and peak acid output (PAO) were determined along with gastrinaemia in 57. Oesophageal manometry was carried out in 14 patients, and oesophageal pHmetry in 13.

Smokers were required to have ceased tobacco consumption entirely, with no oral intake of food for 8 h before surgery. Sodium cephamycin (single dose of 1 g) was given as antibiotic cover 1 h before operation.

Surgical technique

Under general anesthesia, the patient is positioned lying face up with the legs separated (20° anti-Trendelenburg). The surgeon stands between the open legs. The first assistant stands to the left of the patient, with the second to the right.

Five trocars are required for the same number of ports; the uses of the latter vary according to the surgical stage (detailed below): supraumbilical (12 mm; optics); below the right ribcage margin (10 mm; liver fan retractor); below the left ribcage margin (5 mm; grasping forceps); midpoint between the supra-umbilical and left ribcage ports (15 mm; scissors, hook, endoclip, stapler); and subxiphoid (5 mm; grasping forceps, irrigation, aspiration) (*Fig. 1*).

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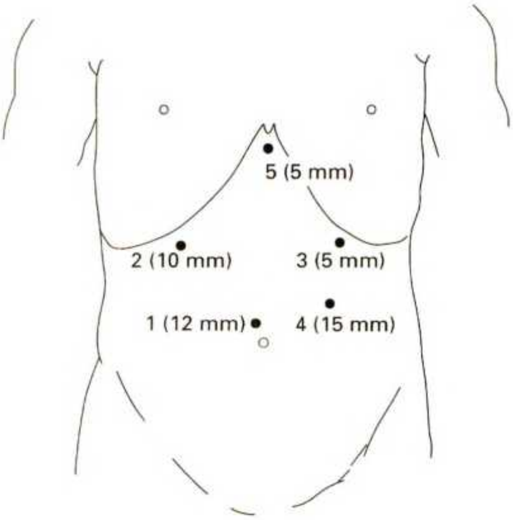

Fig. 1 Ports used for positioning cannulas. 1, Supraumbilical (12 mm); 2, below right costal margin (10 mm); 3, below left costal margin (5 mm); 4, midpoint between supraumbilical and left costal ports (15 mm); 5, subxiphoid port (5 mm)

Posterior truncal vagotomy. After inspecting the entire abdominal cavity, the liver retractor is introduced through the right subcostal port. The first assistant holds the laparoscope with the left hand (umbilical port) and pulls slightly on the stomach to the left to tense the lesser omentum from the left subcostal port.

The surgeon in turn manipulates forceps through the subxiphoid port with the left hand, and coagulating scissors through the left transrectal port with the right hand.

The lesser omentum is sectioned, preserving the pars condensa, together with the phreno-oesophageal membrane. The right diaphragmatic crus is identified and separated from the oesophagus to the left. An intra-abdominal pressure of 13–14 mmHg helps in the dissection. The posterior vagus nerve is identified, together with a possible Grassi criminal nerve (present in 9 per cent of patients)[16]. Whenever located, the coeliac branch is always preserved. The posterior vagus is removed over a length of 1–2 cm, and the specimen is sent for histopathological study.

Anterior linear gastrectomy. The surgeon identifies the crow's foot and grasps it with the right hand through the left subcostal port, using Babcock forceps. This is then held in the first assistant's right hand, while the second assistant pulls on the anterior wall of the stomach 1–2 cm from the cardia towards the diaphragm, through the subxiphoid port. A vertical fold is created as a result. A number of sutures may be placed through the abdominal wall to grasp the gastric wall 1·5 cm from the lesser curve and thus contribute to forming the fold.

An Endo-GIA 30 (Autosuture, Ascot, UK) is introduced through the port situated midway between the supraumbilical and left ribcage ports, and closed to include the first branch of the crow's foot. The instrument is then fired, until a closed gastric tube 1–1·5 cm in diameter is finally created. An Endo-GIA 60 is then introduced and fired two or three times until the cardia is reached. The fundus is freed and retracted, and the linear gastrectomy completed (avoiding displacement to the left) to the uppermost part of the fundus and beyond it, 1·5 cm above the cardia. The surgeon maintains the suture–section line open with the left hand and positions the stapler at the angle formed by the stapled lines. It is important to stay 1–1·5 cm from the lesser curve and to pass 1·5 cm from the cardia, to avoid displacement towards the left side of the stomach (*Figs 2* and *3*).

White vascular cartridges are used to improve haemostasis. Gastric sealing may be evidenced by introducing methylene blue through the nasogastric tube. The specimen is then removed and sent for histopathological study and a simple radiograph is taken to verify that all staples are correctly positioned. The aponeurotic flaps are closed with reabsorbable sutures, and the nasogastric tube is left in place for 24 h. On the second day oral fluid intake is restarted.

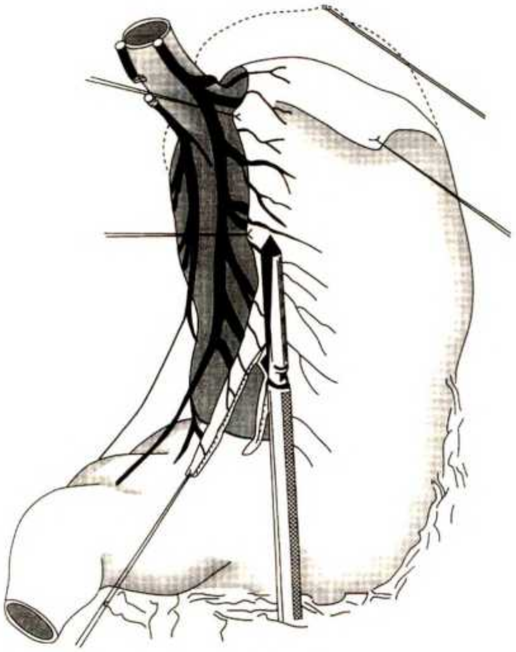

Fig. 2 Oblique view of the stomach, showing the sectioned posterior vagus nerve. Traction sutures are positioned in place of grasping forceps, for clarity. Gastric fundus displacement is also shown

This procedure was combined with laparoscopic cholecystectomy in 16 patients and with laparoscopic Nissen fundoplication in 12.

Results

The mean duration of surgery was 65 (range 25–180) min, and the laparoscopic approach proved feasible in all patients. In all patients undergoing cholecystectomy, and in those subjected to the Nissen operation, the mean surgical time was prolonged by 25 and 40 min respectively. No conversion to open surgery was required, and no serious peroperative complications occurred. Oesophagogastric transit was evaluated in 128 patients, and no contrast leakage was recorded in any patient. In the immediate postoperative period the morbidity rate was 2·9 per cent (one case each of atelectasia, thrombophlebitis, omphalitis and parietal haematoma). Mortality rate was zero and the mean hospital stay was 3·1 (range 2–13) days.

A total of 131 patients were evaluated at 6–33 (mean 25) months. Of these, 126 (96·2 per cent) were rated as Visick I or II; four (3·0 per cent) as Visick III; and one patient (0·8 per cent) as Visick IV, due to asymptomatic ulcer recurrence 4 months after surgery. pH studies were performed in 45 patients before and after operation, with mean BAO and MAO reductions of 78 and 83 per cent respectively, 3 months after the operation. Only 40 of the 86 patients subjected to preoperative endoscopy underwent repeat endoscopy 3–6 months after surgery

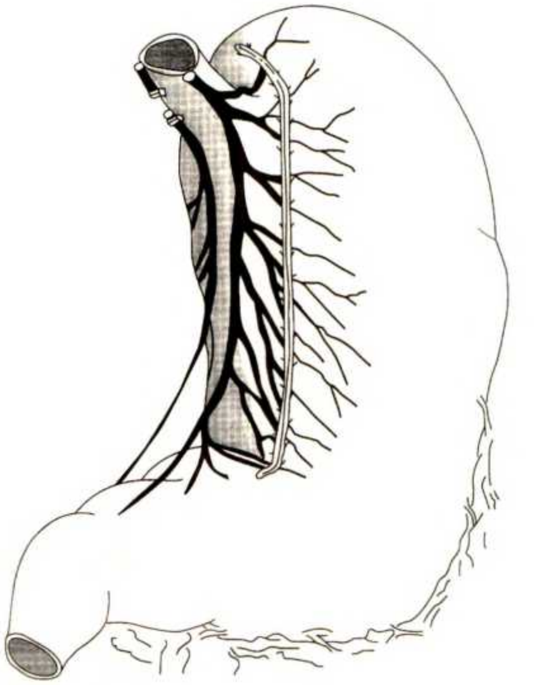

Fig. 3 View of the stomach after resection of the anterior gastric wall. Note the medial displacement of the upper section trajectory, to avoid any mistaken displacement to the left that might leave the innervation partially intact

(many refused postoperative endoscopy or gastric chemisms) and, in all but one patient, ulcer healing was demonstrated. In this single patient, however, pain had disappeared and the condition was under medical control.

Discussion

The efficacy of the medical treatment of duodenal ulcer has been clearly demonstrated. Thus, omeprazole achieves healing in 90 per cent of patients, although recurrences develop in 50–99 per cent when medication is suspended.

Two decades ago most elective surgery in patients with duodenal ulcer was performed to provide relief from drug-resistant pain. At present, and in view of the efficacy of antisecretory and antibiotic treatment, non-urgent indications for surgery are few and include refractory ulcers and recurrences when medication is interrupted.

In 1986 Gómez-Ferrer believed that the surgical literature was lacking in experimental studies on the possible nerve regeneration of the anterior gastric wall following seromyotomy of the lesser curve (Taylor's operation). As a result, his group used 28 rats (including four controls) to compare PTV with anterior seromyotomy (12 animals) and gastrotomy from the crow's foot to the uppermost part of the fundus, followed by eversion suturing (12 animals)[10,11]. Both methods proved effective, although gastrotomy involved sectioning the two intramural gastric plexuses. Moreover, on extending section to the uppermost part of the fundus the branches descending from the intramural oesophageal plexuses were also divided. It was concluded that a fast and safe method for performing gastrotomy with eversion sutures would be to remove a fold from the anterior wall of the stomach, in close proximity to the lesser curve, using a mechanical stapler. Gómez-Ferrer called this procedure ALG[7,8,14,16], and it has been applied in humans during conventional surgery since 1986.

With the aim of establishing the efficacy of the above technique, a second experimental study was carried out in 31 rats to evaluate the pH of gastric secretions on a weekly basis for 3 months after PTV and ALG. Gastric pH was found to be significantly higher than after PTV with seromyotomy. Moreover, there was no wound infection, mortality, diarrhoea or gastric stasis, and all animals increased body-weight normally[12,13]. With the availability of endo-staplers, PTV was performed with ALG in humans, adopting a laparoscopic approach[7–9].

Conventional bilateral truncal vagotomy with pyloroplasty (0·5–0·9 per cent mortality rate, 6–7 per cent recurrence rate, 75–85 per cent Visick I) entails major morbidity in 15 per cent of patients undergoing conventional surgery[17]. In this sense, gastric emptying disorders due to antral hypomotility, absence of the third phase of the interdigestive motor complex with acceleration of the early phase of liquid emptying, and delayed emptying of solids (phytobezoars) are well documented problems[18]. No extensive studies have been published on the results of laparoscopic surgery.

Supraselective vagotomy, when performed by means of open surgery, has a 0·1 per cent mortality rate and offers good results in the immediate postoperative period. However, after 5 years the rate of recurrence reaches 17 per cent, and increases to 27–30 per cent after 10 years, depending on the surgeon's experience[17]. In addition, excellent experimental studies have demonstrated reinnervation after this type of surgery[19,20]. When performed laparoscopically, the procedure becomes tedious and time consuming, except when carried out by a highly expert surgeon, and its reproducibility is consequently low. Ischaemic necrosis of the lesser curve occurs in 1 per cent of patients[21], and Cadiere *et al.*[21] have occasionally observed clip migration towards the stomach interior and two cases of giant ischaemic ulcers affecting the lesser curve. The technique reportedly may also damage Latarget's nerve, and dysphagia frequently results from the dissection of the last 6 cm of oesophagus. Destruction of the anatomical cardial retention mechanisms in turn leads to gastro-oesophageal reflux in 15 per cent of patients; this makes fundoplicature necessary, with the additional morbidity and risks involved[3,21].

PTV and anterior seromyotomy performed laparoscopically is a difficult and time-consuming operation that, moreover, causes important bleeding and is scantly reproducible. It implies the risk of peroperative or late perforation of the gastric mucosa, and nerve regeneration if the sectioned seromuscular component is sutured. In the experimental setting ALG has been found to be more effective than seromyotomy. Despite the good results reported by Katkhouda and Mouiel[6], a number of surgeons no longer perform this operation[22,23].

PTV and ALG, as proposed in the present study, is a simple and rapid technique as dissection is limited to identifying the posterior vagus, and this does not usually pose a problem. As is well known, Grassi's criminal nerve is present in a number of patients and must be looked for[22]. Before this, the crow's foot is identified, working 1–2 cm from the cardias and reaching the uppermost part of the fundus. The technique is safe, as the endo-staplers achieve perfect sealing and haemostasis, and problems have not been encountered with either leakage or bleeding. Moreover, there is no risk of subjecting the lesser curve to ischaemia or of damaging Latarget's nerve. The results of the multicentre study, with 96·2 per cent of patients scoring Visick I or II, may be considered favourable. The data are similar to those already published on seromyotomy and supraselective vagotomy[3,6].

Finally, the method is easy to reproduce laparoscopically, as demonstrated by the fact that, even though costly, it is being adopted by a growing number of surgeons[23,24]. In any case, experience with a greater number of patients must be accumulated, with longer follow-up, to obtain a definitive evaluation.

In the authors' opinion, surgery for chronic duodenal ulcer should be performed laparoscopically. Bilateral truncal vagotomy with drainage and gastrectomy should be avoided as definitive procedures because they are associated with an unacceptably high incidence of side-effects. Proximal gastric vagotomy and seromyotomy are in turn limited by morbidity and surgeon experience, and both are difficult to perform laparoscopically. PTV and ALG constitute a good alternative, considering that recurrences are easier to manage than severe complications.

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Appendix

The following surgeons and institutions contributed patients to the study. Gómez-Ferrer: Hospital Glínico Universitario (Valencia, Spain); Clínica Quirón (Valencia, Spain); Hospital Erasmus (Brussels, Belgium); Hospital Severo Ochoa (Mostoles, Spain) (27 patients). Balique: Centre Hospitalaire Regional Universitaire Bellevue (St Etienne, France) (25 patients). Azagra: C.H.U. Vesale (Montigny-le-Tilleul, Belgium) (23 patients). Bicha-Castelo: Hospital Clínico Universitario (Lisbon, Portugal) (14 patients). Castro-Sousa: Hospital Universitario (Coimbra, Portugal) (12 patients). Espalieu: Clinique de la Jomayère (St Etienne, France) (nine patients). Rodero: Hospital La Fé (Valencia, Spain) (six patients). Estour: Clinique Saint Joseph (Valence, France) (six patients). Múgica: Hospital San Eloy (Baracaldo, Spain) (five patients). Ornelas: Hospital de Fonchal (Madeira, Portugal) (five patients). Sbih: Hospital Birtraria C.H.U. Ouest Alger (Algeria) (six patients). Total: 136 patients.

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Synergistic antitumour effect of recombinant human tumour necrosis factor α with melphalan in isolated limb perfusion in the rat

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The efficacy of isolated limb perfusion (ILP) for 'in-transit' metastases from malignant melanoma and irresectable soft tissue sarcoma has been improved considerably by the addition of tumour necrosis factor (TNF) α. A rat sarcoma tumour model was, therefore, developed to evaluate the effects of TNF-α, melphalan and the combination of these drugs in the treatment of sarcoma. In BN rats bearing the non-immunogenic BN 175 sarcoma ILPs were performed with perfusate only, TNF-α, melphalan alone, or in combination when tumours had grown to approximately 1·5 cm in diameter. All rats treated with sham perfusion or perfusion with 50 μg TNF-α showed progressive disease. After perfusion with 40 μg melphalan no change in tumour diameter was observed in any rats at 4 days. After a combined perfusion with 40 μg melphalan and 50 μg TNF-α complete remission was noted in 12 of 16 rats. This synergistic effect *in vivo* between relatively ineffective doses of TNF-α and melphalan was not observed *in vitro*.

Tumour necrosis factor (TNF) α in combination with interferon γ and melphalan in isolated limb perfusion (ILP) results in a high complete remission rate in patients with 'in-transit' metastases from malignant melanoma[1,2]. Identical treatment has been applied to patients with irresectable soft tissue sarcoma of the limbs in an attempt to render the tumours resectable and thus avoid amputation or disarticulation. An 88 per cent overall response rate with a limb salvage rate of 87 per cent has been reported[3]. ILP was first described by Creech *et al.*[4] and provides high regional drug concentrations with minimal systemic toxicity. Response rates obtained with ILP with conventional cytostatic agents, such as melphalan and doxorubicin, have been disappointing in patients with soft tissue sarcomas[5,6]. This prompted Liénard and co-workers[1] to investigate the addition of high doses of TNF-α in the treatment of irresectable sarcomas.

During ILP, tumours may be exposed to extremely high levels of TNF-α, but the disappointing results from systemic administration of TNF-α in phase I–II trials[7–11] may be because toxicity in humans allows only for the administration of about 1/20–1/50 of the dose required for antitumour effects in murine experimental tumour models[12]. As ILP can achieve a 20-fold increase in concentration of the drug[13], this may be the best way of determining whether TNF-α can be used effectively.

TNF-α as a single agent has only been administered by ILP in a small number of patients in a feasibility study. In this study, therefore, the efficacy of TNF-α, melphalan and the combination thereof was investigated in a rat model of ILP.

Materials and methods

Animals

Male inbred BN strain rats, weighing 250–300 g and obtained from Harlan-CPB (Austerlitz, The Netherlands), were used. The rats were fed a standard laboratory diet (Hope Farms, Woerden, The Netherlands). They were housed under standard conditions of light and accommodation. The experimental protocols adhered to the rules outlined in the Dutch Animal Experimentation Act 1977 and the published Guidelines on the Protection of Experimental Animals by the Council of the European Community 1986. The protocol was approved by the committee on animal research of the Erasmus University, Rotterdam, The Netherlands.

Tumour

The spontaneous BN 175 sarcoma (transplantable to BN rats) was used[14,15] and implanted subcutaneously in the flank and passaged serially. BN 175 sarcoma is a rapidly growing and metastasizing tumour. As determined by the immunization challenge method of Prehn and Main[16], the BN 175 sarcoma is non-immunogenic and can be maintained in tissue culture.

Melphalan

Melphalan (Alkeran, 50 mg per vial; Wellcome, Beckenham, UK) was diluted in 10 ml diluent solvent. Further dilutions were made in 0·9 per cent NaCl to give a volume of 0·2 ml in the perfusion circuit.

Tumour necrosis factor α

Recombinant human TNF-α was provided by Boehringer (Ingelheim, Germany) with a specific activity of 5·8 × 10^7 units/mg as determined in the murine L–M cell assay[17]. Endotoxin levels were less than 1·25 endotoxin units (EU) per mg protein

Tumour model

Fragments (3–5 mm) of the BN 175 sarcoma were implanted into the right hindlimb subcutaneously just above the ankle. Perfusion was performed at a tumour diameter of approximately 15 mm at least 7 days after implantation. Subsequent tumour growth was recorded by calliper measurement. The mean of two perpendicular diameters was obtained. Tumour diameters were measured at least three times weekly.

The classification of tumour response was: progressive disease (increase in tumour diameter more than 25 per cent within 4 days; no change (tumour diameter equal to diameter during

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perfusion (range −50 to +25 per cent)); partial remission (decrease in tumour diameter of less than −50 per cent; complete remission (no tumour palpable). When complete remission was associated with skin necrosis at the tumour site this response was classified as CR_{SN}.

Isolated limb perfusion

Modification of the perfusion technique originally described by Benckhuijsen *et al.*[18] was used. Briefly, animals were anaesthetized with Hypnorm (Janssen Pharmaceutica, Tilburg, The Netherlands) and 50 units heparin was injected intravenously. To keep the rat's hindleg at a constant temperature of 38–39°C, a warm water mattress was applied. The femoral artery and vein were cannulated with silastic tubing (0·30 mm inner diameter, 0·64 mm outer diameter; 0·64 mm inner diameter, 1·19 mm outer diameter respectively; Dow Corning, Michigan, USA). Collaterals were occluded by a groin tourniquet and isolation time commenced when the tourniquet was tightened. An oxygenation reservoir and a roller pump were included in the circuit. The perfusion commenced with 5 ml Haemaccel (Behring Pharma, Amsterdam, The Netherlands), and the haemoglobin content of the perfusate was 0·9 mmol/l. Melphalan and TNF-α were added as boluses to the oxygenation reservoir. A roller pump (Watson Marlow, Falmouth, UK; type 505 U) recirculated the perfusate at a flow rate of 2·4 ml/min. A washout with 2 ml oxygenated Haemaccel was performed at the end of the perfusion. In the rat collateral circulation via the internal iliac artery to the leg is so extensive that it allows ligation of the femoral vessels without detrimental effects and, after ligation of the femoral artery, backflow from the femoral vein was seen in all rats immediately after release of the tourniquet. The partial pressure of oxygen (P_{aO_2}) was similar before and after ligation of the femoral vessels[19].

In vivo *tumour response studies*

Experiments were performed in five groups of rats; group 1, sham perfusion ($n = 9$); group 2, melphalan perfusion with total doses of 40 μg ($n = 4$), 0·2 mg ($n = 6$) and 1 mg ($n = 4$); group 3, perfusion with 40 μg melphalan ($n = 5$); group 4, perfusion with 50 μg TNF-α ($n = 9$); group 5, perfusion with 40 μg melphalan and 50 μg TNF-α ($n = 16$). (Previous studies have shown that perfusions with even 100 μg TNF-α have no antitumour effects[19].)

Histology

For histopathological studies an additional 16 rats were used; four per group were sacrificed 24 h after treatment. Tumours were excised and fixed in 4 per cent formaldehyde solution and embedded in paraffin. Sections of the tumour were stained with haematoxylin and eosin

In vitro *assessment of antitumour activity*

BN 175 sarcoma grows as a monolayer in Dulbecco's modified Eagle's medium containing 5 per cent fetal calf serum and glutamic acid 0·3 mmol/l (Gibco, Paisley, UK). The sulphorhodamine B protein stain assay was used according to the method of Skehan *et al.*[20]. Eight replicate experiments were performed. Tumour growth was calculated using the formula: tumour growth = (test well/control) × 100 per cent. The drug concentration reducing the absorbance to 50 per cent of control (IC_{50}) was determined from the growth curves Sensitization ratios of combinations of melphalan with TNF-α were determined by dividing the IC_{50} in the presence of the single agent by the IC_{50} in the presence of the additional agent.

Statistical analysis

To compare tumour diameters in different animal groups the Mann–Whitney *U* test and Student's *t* test were used.

Results

Dose ranging for melphalan

Perfusions were performed with 1 mg, 0·2 mg and 40 μg melphalan. Perfusions with 1 mg melphalan resulted in tumour regression consisting of two of four partial remissions and two of four complete remissions. Remission was characterized by a gradual disappearance

Table 1 Antitumour effects of isolated limb perfusion in the BN 175 sarcoma model

	Sham perfusion	Perfusion with 50 μg TNF-α	Perfusion with 40 μg melphalan	Perfusion with 50 μg TNF-α and 40 μg melphalan
Progressive disease	9	9	0	0
No change	0	0	9	4
Partial remission	0	0	0	0
Complete remission	0	0	0	3
Complete remission and skin necrosis	0	0	0	9
Total	9	9	9	16

TNF-α, tumour necrosis factor α

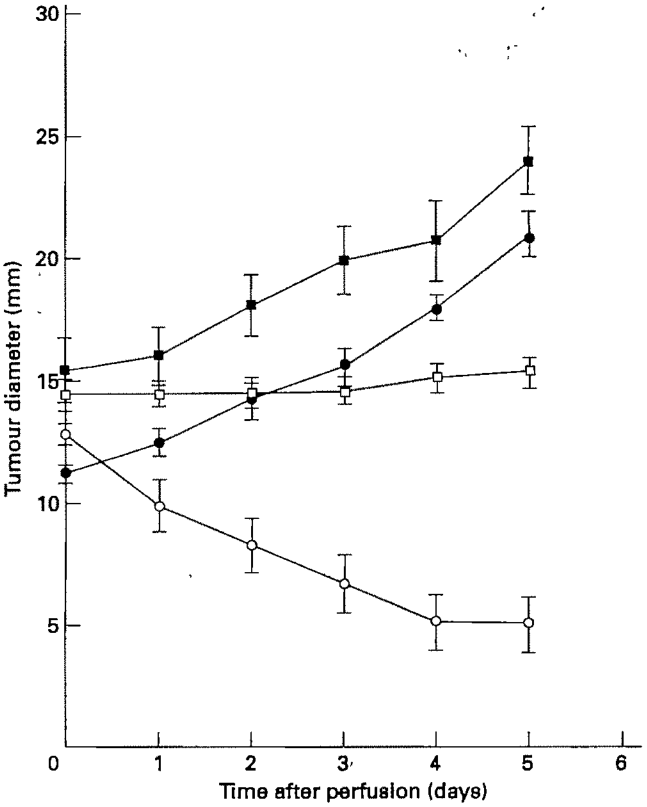

Fig. 1 Growth curves of hindlimb BN 175 sarcoma after sham perfusion (■; $n = 9$), 50 μg tumour necrosis factor (TNF) α (●; $n = 9$), 40 μg melphalan (□; $n = 9$), and TNF-α plus melphalan (○; $n = 16$). Values are mean(s.e.m.) of tumour diameters. At day 5 after perfusion: combined *versus* melphalan group, combined *versus* TNF-α group, and melphalan *versus* TNF-α group show significant differences ($P < 0·001$, Mann–Whitney *U* test and Student's *t* test). No significant difference was apparent between the TNF-α and sham groups ($P > 0·05$, Mann–Whitney *U* test and Student's *t* test)

of tumour without darkening of the skin. Atrophy of the musculature occurred. In only one rat was a long-lasting complete remission obtained (sacrificed at day 105). Perfusion with 0·2 mg melphalan resulted in no change for four of six tumours and two of six complete remissions without marked atrophic changes in the hindleg. Perfusion with 40 μg melphalan inhibited tumour growth for at least 4 days in four of four rats (*Table 1*).

Tumour response study

Results are summarized in *Table 1*. Sham perfusion and perfusion with TNF-α did not inhibit tumour growth and progressive disease was observed in all rats in both groups. After perfusion with 40 μg melphalan tumour growth was arrested in all five animals for at least 4 days. Complete tumour remission occurred after combined perfusion with 50 μg TNF-α and 40 μg melphalan in 12 of 16 rats; nine of the complete remissions were classified as CR_{SN}. Recurrences were noted in eight of 16 rats. Eight rats did not have recurrences, but these rats had to be killed as they developed skin necrosis at the tumour site.

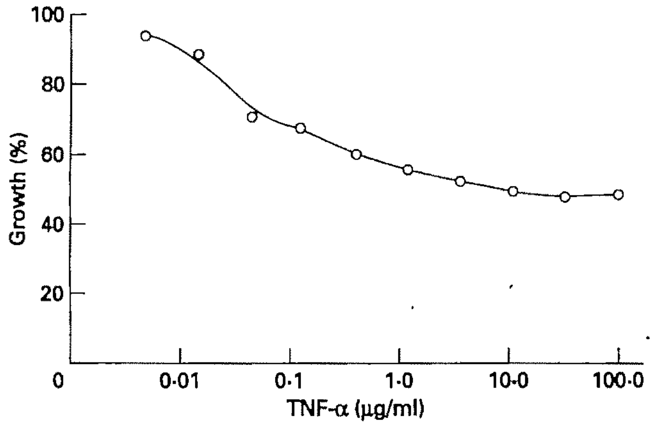

Fig. 2 Dose/response curve of BN 175 sarcoma to tumour necrosis factor (TNF) α determined in the sulphorhodamine B assay

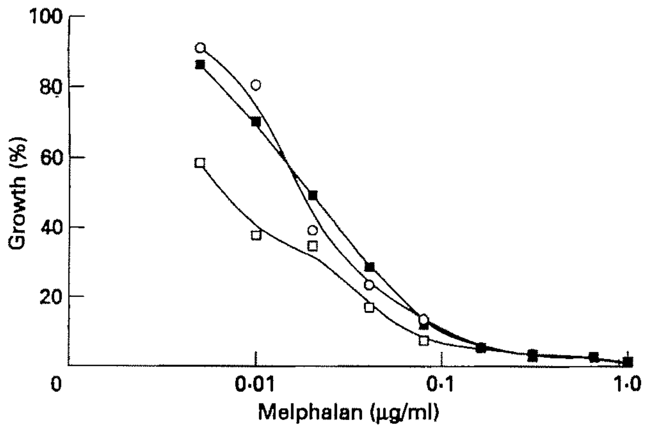

Fig. 3 Dose/response curve of BN 175 sarcoma to melphalan in the absence of tumour necrosis factor (TNF) α (■), in the presence of 0·1 μg/ml TNF-α (○), and 1·0 μg/ml TNF-α (□), determined in the sulphorhodamine B assay

Regrowth of tumour was usually seen about 11 days after perfusion (mean(s.d.) 10·9(2·8) days). In *Fig. 1*, growth curves of all treatment groups are shown.

Histology

In non-perfused tumours and those harvested 24 h after sham and melphalan ILP oedema, dilated vessels and lymphocytes, scattered through the tumour, were found. Haemorrhagic and ischaemic necrosis were absent or limited to less than 5 per cent. In addition, rats treated with TNF-α and the combination of melphalan and TNF-α demonstrated haemorrhagic necrosis in the central part of the tumour. In rats treated with TNF-α and melphalan haemorrhagic necrosis was much more extensive than in rats receiving ILP with TNF-α alone. In two rats margination of polymorphonuclear cells in the tumour vessels with increased influx into the tumour was observed.

In vitro *cytotoxicity assay*

The *in vitro* dose/response curve of BN 175 sarcoma cells to TNF-α is depicted in *Fig. 2*. In *Fig. 3* the dose/response curves with melphalan alone or combined with 0·1 and 1·0 μg/ml TNF-α are depicted. The IC_{50}s were equivalent for 0 and 0·1 μg/ml TNF-α, but attenuated in the presence of 1·0 μg/ml TNF-α. The mean(s.d.) sensitization ratio in the presence of 1·0 μg/ml TNF-α was 2·9(0·5) calculated from three different experiments. As 1·0 μg/ml TNF-α alone can reduce tumour growth to 55 per cent, the enhanced cytotoxicity is probably due to additive effects.

Discussion

These experiments have shown that TNF-α is only effective when administered in combination with melphalan. Isolated limb perfusion with perfusate alone or 50 μg TNF-α alone had no impact on tumour growth and 40 μg melphalan only temporarily inhibited tumour growth. In the groups perfused with the combination of both complete remission occurred in 12 of 16 rats. Histologically, haemorrhagic necrosis was observed after ILP with TNF-α alone but this was much more extensive with the combined treatment.

Interaction of the two agents on direct tumour cytotoxicity could be one explanation for the *in vivo* synergism observed. *In vitro* studies demonstrated no synergy, but an additive effect at best. All observations therefore indicate that the *in vivo* antitumour effects are mediated by indirect mechanisms such as effects on the tumour-associated vasculature (TAV); increased penetration of the cytostatic agent by these effects on TAV; and the immune system.

Disappearance of the tumour within 2–3 days together with the histological observation of haemorrhagic necrosis are typical of TNF-α treatment based on the vascular effects reported in many experimental studies[21–23]. Increased endothelial permeability, erythrostasis and thrombocyte aggregation, followed by vascular occlusion and haemorrhagic necrosis have been described in tumours treated with ILP and TNF-α in patients[24]. Moreover, preferential occlusion of all the TAV has been demonstrated angiographically in patients after ILP[25]. Combination of TNF-α with melphalan resulted in remission, which was associated with extensive haemorrhagic necrosis of the tumour within 24 h of ILP. This suggests a potentiating role of melphalan on the effects of TNF-α on the TAV. For extensive haemorrhagic necrosis to occur, another detrimental agent in addition to TNF-α was apparently necessary. As with the alkylating agent cyclophosphamide, melphalan may well induce damage to endothelial cells[26].

Better penetration of the therapeutic agents may result from increased permeability of TAV induced by TNF-α. The synergism of specific immune therapy and cyclophosphamide in a guinea-pig metastasis model was also found to be associated with vascular leakage within tumours[27]. In recent studies the accessibility of monoclonal antibodies was increased after the administration of TNF-α[28]. Based on these reports, melphalan delivery to the tumour may be enhanced by TNF-α.

For sequential biopsies in patients, changes in TAV are associated with leucocyte infiltration in the tumour[29]. By contrast, in the present rat model increased polymorphonuclear cell margination and influx was not uniformly present in the areas of haemorrhagic necrosis. In previous studies in mice polymorphonuclear cells and macrophages have been implicated in the induction of haemorrhagic necrosis by TNF-α[30,31]. As distinct from their role in early TNF-α effects such as haemorrhagic necrosis, inflammatory cells are probably of crucial importance in tumour regression in later phases[32]. However, this has only been shown to be the case in immunogenic and not in non-immunogenic tumours[12]. As a non-immunogenic tumour was used, it is likely that a second step immune reaction following haemorrhagic necrosis may not be relevant in this model. In non-immunogenic tumours, a viable rim of tumour is suggested to replace the central haemorrhagic necrosis in the tumour[12]. This explains the lack of tumour regression, despite haemorrhagic necrosis, found after ILP with TNF-α alone in this model.

In conclusion, these experiments have revealed synergism between TNF-α and melphalan with a 75 per cent complete response rate. The model appears, therefore, to be clinically relevant. The synergy observed is mainly mediated by indirect antitumour mechanisms such as the destruction of TAV and consequently an enhanced efficacy of melphalan. Further elucidation of the mechanisms involved will be necessary to allow development of treatment programmes and to extend isolated perfusion with TNF-α to the treatment of other tumours such as those in the liver and lung[33,34].

Acknowledgements

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The Vascular Surgical Society of Great Britain and Ireland

The following abstracts are from the papers presented at the 29th Annual Meeting of the Vascular Surgical Society of Great Britain and Ireland, held in London, UK, on 16–17 November 1995. President of the Society, Mr Crawford Jamieson, was in the chair.

Early experience of free flaps in patients undergoing femorodistal bypass surgery

D. J. A. Scott, S. Knight, D. C. Berridge, J. I. Spark and N. Horlock, *St James's and Seacroft University Hospital, Leeds, UK*

Free tissue flaps are a recognized technique for covering exposed bone and or skin defects. Their role in patients with critical ischaemia is uncertain. This abstract describes the 'learning experience' of free flaps in patients with critical ischaemia, and reviews an initial experience of ten patients undergoing 11 free flaps following femorodistal bypass for critical ischaemia between January 1994 and June 1995.

There were nine men and one woman of median age 68 (interquartile range (i.q.r.) 62–71) years who had a total of 11 free flaps. Eight patients had diabetes (three insulin dependent, five diet controlled), three had cardiac disease and three a previous amputation. All ten patients had undergone vascular surgery for critical ischaemia, three as a simultaneous procedure with the free flap. There were three femoropopliteal bypass grafts (two reversed vein graft (RVG), one polytetrafluoroethylene), three femoroanterior tibial RVGs, two femoroposterior tibial RVGs (lower third of the calf), one femorolateral plantar RVG with a graft extension to the dorsalis pedis, and two popliteal dorsalis pedis RVGs. There were six lateral arm flaps, three latissimus dorsi, one scapular and one radial forearm flap. All flaps were performed for exposed bone and tendon. The arterial anastomosis was performed end to end (EE) to the dorsalis pedis in seven cases, vein graft (end to side) in three, medial plantar (EE) in one and to the first metatarsal artery (EE) in one. Venous anastomoses were performed to the adjacent vanae committans.

There was one acute free flap failure at 24 h due to venous thrombosis. One patient occluded a repeat popliteal dorsalis pedis graft at 5 days with subsequent loss of the flap and in another the distal anastomosis of a popliteal dorsalis pedis graft failed at 10 days with subsequent loss of the flap. Three further flaps were lost at 6, 8 and 32 weeks following graft occlusion, with subsequent loss of the limb (two above-knee and one below-knee amputations). Five free flaps remain viable in four patients at a median of 7 (i.q.r. 4–9) months; all four patients are mobile and independent at home. One patient developed a midgraft vein stenosis which was initially treated by balloon angioplasty and later by an interposition vein graft. The 30-day mortality rate of these combined procedures is zero. However, one patient died 4 months after surgery from a myocardial infarct.

In conclusion, free tissue flaps are an effective method of closing defects in the foot following digital or transmetatarsal amputation. The lateral arm flap is preferred because of its ease of use, long vascular pedicle and low donor site morbidity. The use of free flaps to improve the run-off from a femorodistal bypass is associated with graft failure and loss of limb.

Hyperhomocysteinaemia: a risk factor for vein graft stenosis

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Autogenous vein remains the conduit of choice for infrainguinal bypass grafting but up to 30 per cent of vein grafts fail within the first year. Excluding technical errors, most failures are due to progressive vein graft stenosis (VGS) from intimal hyperplasia. Systemic factors have been implicated in the aetiology of intimal hyperplasia. Hyperhomocysteinaemia is established as an independent risk factor for coronary and peripheral arterial disease. The aim of this study was to compare serological factors, including plasma homocysteine concentration, in patients with and without VGS.

To date 38 patients who have undergone infrainguinal vein bypass have been recruited to a case–control study from a graft surveillance programme. Nineteen patients with documented VGS were matched against controls without stenosis for age, sex, length of time from surgery, diabetes, smoking history and preoperative symptom score. All patients were recalled for check duplex ultrasonography, venesection and carbon monoxide estimation. Biochemical and haematological parameters were measured as well as estimation of plasma homocysteine with a previously validated assay. Duplex scans and blood tests were performed blind.

Statistical analysis of all parameters was carried out with a Wilcoxon signed rank test (95 per cent confidence limits). Plasma homocysteine was significantly raised in patients with VGS. Results are presented as median (interquartile range) and the laboratory normal range is given.

	VGS group	Control group	Normal range
Median plasma homocysteine (μmol l^{-1})	17·8* (13–22)	13·8 (11–18)	9·5 (8·5–10·6)

**P* < 0·03 *versus* controls (two-tail probability)

The only other significant association with respect to lipid and thrombophilia profiles was a low lipoprotein level in the VGS group.

These results suggest that hyperhomocysteinaemia is a previously unidentified risk factor for VGS. Patients with hyperhomocysteinaemia are susceptible to VGS, allowing the prospect of therapeutic intervention with folate, which is known to reduce serum homocysteine levels.

Duplex surveillance of infrainguinal vein grafts improves patency but not limb salvage

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Graft surveillance has many implications, both clinical and financial, with respect to patency and limb salvage. The objectives of this study were to assess the impact of duplex surveillance on the results of infrainguinal vein grafts.

A meta-analysis has been performed comparing the outcome of vein grafts under duplex surveillance with that of those under clinical follow-up. Only studies providing information on occlusion rates were included. Mortality and limb salvage rates were also analysed but were not available from all studies.

A total of 2680 surveillance and 3969 non-surveillance vein grafts were analysed. There was no significant difference between the two groups with respect to presence of critical ischaemia ($P = 0·1$) and level of distal anastomosis ($P > 0·5$). Surveillance identified 493 stenoses in 469 grafts (18 per cent); 397 grafts (15 per cent) were treated by surgery (248; 62 per cent) and angioplasty (149; 38 per cent). Ninety-eight grafts (25 per cent) developed recurrent stenosis.

The total number of deaths, total number of occluded grafts and number of occlusions after 30 days were significantly greater for the no surveillance group ($P<0{\cdot}001$, $P<0{\cdot}001$ and $P<0{\cdot}01$ respectively). Perioperative occlusion rates were not significantly different ($P=0{\cdot}05$). Only six of the 17 surveillance studies reported amputation rates. Above- or below-knee amputation was required in 85 (13 per cent) of 664 patients under surveillance and in 357 (13 per cent) of 2842 having no surveillance ($P>0{\cdot}5$).

The patency of infrainguinal vein grafts would appear to be improved as a result of surveillance. However, no improvement in limb salvage has been demonstrated.

Amputation rates in England over a 5-year period

H. M. Hafez, J. H. N. Wolfe and G. Stansby, *St Mary's Hospital, London, UK*

In spite of good results from individual centres, there continues to be controversy over the impact of vascular surgical activity on lower limb salvage at a national level. Several studies have reported a rise in amputation rates in recent years despite increased vascular surgical and radiological activity. To date, no such data have been available for England. Data were obtained from a random 25 per cent sample relating to major lower limb amputations between 1989 and 1994 from the Department of Health Central Computer. Data were analysed into above-knee (AKA) and below-knee (BKA) amputations in diabetics and non-diabetics, as shown in the *Table*.

	Non-diabetics			
Year	AKA	BKA	Other*	Total
1989–1990	506	397	102	1005
1990–1991	509	454	91	1054
1991–1992	624	583	120	1327
1992–1993	599	517	123	1239
1993–1994	675	449	94	1218

Diabetics				
AKA	BKA	Other	Total	Total
47	125	6	178	1183
42	96	7	145	1199
62	132	7	201	1528
63	145	12	220	1459
68	143	12	223	1441

*Through-knee and re-do amputations

These data demonstrate that major amputation rates are still rising in England in both diabetics and non-diabetics. These findings have major implications for the future funding and structure of vascular services in England.

Use of anastomotic vein patches in polytetrafluoroethylene bypass grafting: investigation in an experimental model

A. Loh, R. S. Taylor and J. A. Dormandy, *St George's Hospital, London, UK*

The use of anastomotic vein patches has been reported to improve the results of polytetrafluoroethylene (PTFE) bypass grafting, especially in the infrapopliteal position. The reasons for this are unclear and few if any clinical or experimental data have been obtained to support their use. A sheep model of bilateral carotid PTFE bypass grafting with a high failure rate has been developed and three randomized experiments were performed to try to address the question of why anastomotic vein patches improve the patency of PTFE grafts.

In experiment 1, PTFE bypass grafting with direct end-to-side anastomosis on one side was compared with a vein-patched anastomosis on the other ($n=10$). In experiment 2, vein-patched grafts were compared with grafts similarly patched with PTFE on the other side. In experiment 3, 12 vein-patched grafts were compared with similarly patched grafts on the other side but made less compliant by the addition of a PTFE patch over the vein patch.

In experiment 1, non-patched grafts occluded more often than vein-patched grafts, this occurring in six of the ten animals ($P=0{\cdot}03$, sign test). The duration of patency was also significantly longer in vein-patched grafts (mean 10·2 *versus* 8·3 weeks; $t=2{\cdot}62$, $P<0{\cdot}05$, paired t test). Despite occlusions occurring three times more often in non-patched grafts (60 *versus* 20 per cent), this was not significantly different ($P=0{\cdot}08$). The incorporation of a PTFE patch in experiment 2 did not improve results, with the vein-patched grafts having a longer patency (mean 11·1 *versus* 8·2 weeks; $t=2{\cdot}69$, $P<0{\cdot}05$). As in experiment 1, PTFE-patched grafts were the first to occlude in six of 12 animals ($P=0{\cdot}03$). There was no difference in length of patency in experiment 3, with vein-patched grafts showing no advantage over similar grafts made less compliant by the addition of a PTFE graft.

These experiments indicate that, in this sheep model, the addition of anastomotic vein patches improves the length of patency in PTFE grafts (experiment 1). This improvement does not seem to be due to the widening and streamlining of the anastomosis by a patch but to some property of the vein itself (experiment 2). Decreasing the compliance of the vein patch in experiment 3 did not appear to affect the patency rates, and it is therefore more likely that the improvement in results is related to the endothelial lining of the vein patch rather than its physical elastic properties.

Prospective audit of acute leg ischaemia from a single county

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An audit of acute leg ischaemia was designed using multisource data collection from general practitioners, nursing and residential homes, health authority records, and community and district general hospitals. Data were collected on the process of referral, delivery of care and outcome for 1 year (1994) in a single county of population 540 000.

A total of 77 patients (84 episodes) were identified, an incidence of 1 per 8000 population per year for native vessel and 1 per 6000 per year for all episodes of acute leg ischaemia including graft thrombosis.

Of the 77 patients, 73 were identified by hospital records and 22 via the community. Only four patients were not admitted to hospital and were identified from community records alone; all were treated conservatively after telephone discussion with a vascular surgeon, and two died.

Sixty of the 84 events were referred directly to a vascular surgeon, six were referred to the medical team and 13 to the elderly care team with a variety of other diagnoses, e.g. cardiac arrest and collapse. Six of the patients not referred to a vascular surgeon clearly had acute leg ischaemia on admission, while the remaining 13 developed the condition while an inpatient.

Active treatment was undertaken in 65 patients, initially using thrombolysis (33), surgery (28) and stenting (one). Three patients had a primary amputation and 15 had conservative treatment. Outcome of the 80 hospital events after 30 days was limb salvage in 54 (68 per cent), amputation in six (8 per cent) and death in 20 (25 per cent). Ten of the deaths were in patients treated conservatively.

The present audit shows that, in Gloucestershire, almost all patients with acute leg ischaemia are treated by specialist vascular surgeons. Despite an active integrated policy of thrombolysis and surgery, the mortality rate was high (26 per cent of the 84 events), although mostly in patients treated conservatively. These patients might not normally be reported in a clinical study.

Role of hypercoagulable abnormalities in the postoperative failure of arterial reconstruction for leg ischaemia

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Hypercoagulable abnormalities, such as low levels of proteins C and S, antithrombin III, lupus anticoagulant and heparin-induced platelet aggregation, predispose to spontaneous venous and arterial thrombosis. There are now reports suggesting an association between such abnormalities and failure of arterial reconstruction, but this has not been adequately evaluated by prospective investigations.

Between January 1992 and November 1993, 60 patients undergoing elective arterial revascularization for leg ischaemia were recruited. Preoperative measurement of antithrombin III, protein C and S levels, and tests to detect the lupus anticoagulant, were performed, and repeated on the first and third postoperative days and after 1 and 6 months. Heparin-induced platelet aggregation (HIPA) was also sought if the platelet count decreased more than $100 \times 10^{9}\,l^{-1}$ after operation. At each visit patency was ascertained by sustained ankle:brachial pressure index improvement, with arteriography where doubtful. In January 1994 multivariate analysis was performed to ascertain the influence of accepted risk factors for occlusion, as well as preoperative hypercoagulable abnormalities for subsequent patency.

Twenty patients (33 per cent) suffered failure of reconstruction (median interval 2 weeks) while 40 procedures (67 per cent) remained patent (median follow-up 6 months). Twenty-three preoperative hypercoagulable abnormalities were detected in 19 patients (32 per cent) (ten low protein S, nine lupus anticoagulant, three low protein C, one low antithrombin III level) and postoperative HIPA was detected in a further two. The nature of and indications for surgery, or prevalence of smoking and diabetes, were not associated with the outcome of reconstruction. By contrast, preoperative hypercoagulable abnormalities were three times more common before procedures that subsequently failed (65 *versus* 20 per cent; odds ratio 6·6, $P<0{\cdot}01$) and were detected in 11 of 12 patients suffering occlusion within 1 month. Lupus anticoagulant was the preoperative abnormality most associated with failure (positive predictive value 67 per cent, $P<0{\cdot}01$).

Hypercoagulable abnormalities in patients requiring arterial reconstruction are more common (32 per cent) than previously thought. They are an independent risk factor for early failure (odds ratio 6·6) and should be routinely assessed before elective vascular operation.

Is the outcome of femorodistal bypass for critical limb ischaemia predictable?

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In the past decade the number of bypass grafts to single calf or ankle vessels has increased significantly. However, there is great variation in the reported results which may be explained by differences in patient selection. The aim of this study was to develop a predictive scoring system, based on the combination of factors that affect outcome.

A retrospective analysis was undertaken of 109 consecutive femorodistal bypasses performed between June 1991 and December 1994 by a single vascular surgeon, using an aggressive surgical policy.

Complete data were available for all patients, who were followed for 0–42 (median 12·1, mean 15·4) months. All procedures were undertaken as an 'intention to save the limb', provided there was a single calf or pedal vessel shown on preoperative digital subtraction angiography. Preoperative angiograms were reviewed by a surgeon and a radiologist and the state of inflow and run-off was characterized. The Kaplan–Meier method was used for life-table analysis and actuarial curves were compared with Wilcoxon and log rank tests. Factors proven to affect the outcome significantly were inflow state, number of calf run-off vessels, graft material, diabetes, straight flow to the foot and patent pedal arch.

The above variables were weighted according to their significance and a scoring system (ranging from 0 to 10) was developed. Fifty-seven patients with a preoperative score of 0–6 showed a secondary patency rate of 38·2 per cent at 3 months, 8·9 per cent at 12 months, and falling to zero at 16 months (cumulative standard error 7·44). The respective values for the 52 patients with a score of 7–10 were 90·9 per cent at 3 months, 70·7 per cent at 12 months and 63·6 per cent at 2 and 3 years (cumulative standard error 7·50). The difference was highly significant (odds ratio 16, $P=0{\cdot}0001$) in all tests of equality. In addition, the median total hospital cost for the two cohorts was £12 100 and £6600 respectively.

This simple preoperative scoring system is able to predict the outcome of distal revascularization. Furthermore, if applied to the selection of patients, it can dramatically reduce the hospital cost per leg saved. A prospective study to verify the efficacy of the scoring system is now under way.

Controlled randomized study of an oral prostacyclin analogue (iloprost) in patients with inoperable stage III and IV leg ischaemia

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As far as the authors are aware this is the first randomized prospective placebo-controlled trial of an oral prostacyclin analogue in patients with severe arterial disease of the leg. A number of reports have now been published showing some benefit of daily intravenous infusions of prostacyclin analogues, but orally active compounds have not previously been tested.

Some 178 patients with rest pain, ulcers or gangrene of the leg due to arterial disease were randomized to placebo, low-dose or high-dose oral iloprost twice a day for 4 weeks. Low dose was up to 100 g and high dose up to 200 g depending on tolerability. Patients suitable for any reopening procedure were excluded. Patients were followed for 6 months after the end of therapy.

Patients were recruited in 34 European centres. Information about all patients but one (177) was available for analysis in terms of death or amputation at the end of follow-up. Both major amputation and deaths were more frequent in the placebo group than in either treatment group. On an intention-to-treat analysis the percentage of patients who had either died or required a major amputation was 66 per cent in the placebo group and 48 per cent in both the low-dose and the high-dose oral iloprost groups. This difference of 18 per cent was not significantly different. However, if the response of patients who did not die or need a major amputation is taken into account, then the proportion of patients alive without an amputation, ulcers, gangrene or rest pain was 11 per cent in the placebo group compared with 19 per cent in the low-dose and 28 per cent in the high-dose iloprost groups ($P<0{\cdot}05$).

Oral iloprost is safe, has fewer side-effects than the intravenous preparation and appears to have a beneficial effect in terms of amputation and mortality rates during 6 months' follow-up, similar to the intravenous route. The oral presentation should therefore be tested over longer periods of treatment to observe whether this provides further clinical benefit.

Early results of endovascular abdominal aortic aneurysm repair

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Transfemoral endovascular abdominal aortic aneurysm repair was carried out on 44 patients with a median age of 68·5 (interquartile range (i.q.r.) 62–77) years and aneurysm diameter of 6 (i.q.r. 5·4–6·6) cm. Twenty-four of the 44 patients were considered to be high risk and unsuitable for conventional surgery, and 16 of these were referred by other centres.

Preoperative assessment included spiral computed tomography (CT) using multiplanar reconstruction and calibrated aortography. Modified Gianturco stent (Cook), Verisoft Dacron graft (Meadox Medicals) and Wallstent (Schneider) were used. The procedure was performed in the operating theatre under general anaesthesia. An aortouni-iliac graft was used in 29 patients, bifurcated in 13 and aortoaortic in two. Emergency repair for leaking aneurysms was successfully performed in two patients.

Endovascular repair was carried out successfully in 38 of the 44 patients and four required exposure of aneurysm and placement of external ligatures to achieve a seal around the proximal stent. In a further two patients inaccurate deployment necessitated removal of the endoprosthesis and replacement with a conventional graft. Successful endovascular procedures had a median duration of 160 (i.q.r. 120–210) min with a median operative blood loss of 500 (i.q.r. 500–550) ml; all these patients were mobile and resumed normal diet within 48 h. Following elective repair the mortality rate within 30 days was three of 42. All deaths occurred in the high-risk group following open intervention. At a median follow-up of 6·5 (i.q.r. 2–11) months, 40 of 44 patients remain alive and well The graft remains in satisfactory position in all cases. In three patients there remains localized flow of contrast through the aneurysm sac on CT.

Early results indicate that endovascular aneurysm repair is associated with rapid recovery and low morbidity and mortality rates. It is less traumatic and the majority of patients deemed unfit for open surgery can safely undergo endovascular repair. However, at this stage there remains a 10 per cent conversion rate and a similar risk of mortality for this group.

Comparison of magnetic resonance angiography, computed tomography, colour duplex scanning and arteriography for assessing abdominal aortic aneurysms before endoluminal repair

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A detailed assessment of the abdominal aorta is essential for determining patient suitability for endoluminal repair and accurate sizing of the intraluminal prosthesis. Conventional methods of assessment such as ultrasonography and computed tomography (CT) are inadequate.

The aim of this prospective study was to assess the ability of CT, magnetic resonance angiography (MRA), colour duplex scanning (CD) and intra-arterial angiography to visualize abdominal aortic aneurysm (AAA) morphology.

Seventy-seven consecutive patients with AAA (61 men, 16 women) of median age 74 (range 59–87) years underwent CT and MRA. Of these, 55 also had CD and 32 underwent arteriography. The median AAA diameter was 5·7 (range 3·5–9·7) cm. The scans were assessed by two independent blinded observers. The ability of each test to visualize the following parameters was determined: proximal aneurysm neck, tortuosity of aneurysm sac, distal aneurysm neck and iliac arteries. The results are presented as the percentage of patients in whom the above parameters could be visualized with each investigation.

Parameter	CT	MRA	CD	Arteriography
Right renal artery	64	91	51	100
Left renal artery	78	97	51	100
Proximal neck length	81	95	51	78
Maximum anteroposterior diameter	100	100	98	63
AAA sac tortuosity	0	100	95	97
Distal neck length	92	99	95	59
Tortuosity of iliacs	0	91	85	100
Diameter of iliac arteries	91	84	78	100

These results show that MRA is significantly better ($P < 0·05$) at visualizing AAA morphology in comparison with CT and CD. There was no significant difference between MRA and arteriography. Therefore, use of MRA is recommended for determining patient suitability for endoluminal repair

Can lower limb colour-coded duplex scanning safely replace diagnostic arteriography?

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As a result of technological advances and increasing operator expertise, it is now possible to map out the arterial tree in many patients with lower limb arterial disease. The authors therefore decided to abandon diagnostic arteriography in favour of colour-coded duplex scanning as the first-line investigation of lower limb arterial disease, and the purpose of this study was to assess the safety and efficacy of this approach. Over a 1-year period, 423 consecutive limbs have been assessed from aorta to ankle by duplex scanning. The indication for investigation was claudication in 75 per cent, rest pain in 15 per cent, and tissue loss in 10 per cent.

Duplex examinations were technically successful in 394 limbs (93 per cent), with failure due to inability to insonate the iliac arteries in three limbs (1 per cent) and calf vessels in 26 (6 per cent). On the basis of duplex findings, 12 limbs (3 per cent) were referred for diagnostic arteriography because of an inadequate duplex examination, 170 (40 per cent) were managed conservatively, 201 (48 per cent) were referred for angioplasty and 40 (10 per cent) underwent surgical intervention There was an unexpected finding in only five (2 per cent) of 201 limbs referred for angioplasty and in only nine (10 per cent) of 86 limbs with saphenofemoral artery (SFA) occlusions was there disagreement concerning the presence or absence of an SFA stump. There were no unexpected findings in those referred for surgery.

It is concluded that colour-coded duplex scanning can replace diagnostic arteriography in up to 98 per cent of patients with lower limb arterial disease and that patients can safely be referred for either angioplasty or reconstructive surgery on the basis of duplex findings alone.

Deterioration in visual function in patients undergoing carotid endarterectomy

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Amaurosis fugax (AF) is one of the commonest embolic symptoms described by patients presenting with carotid artery stenosis but few studies have addressed the clinical effect of microembolization on visual function. Carotid endarterectomy (CEA) provides a clinical setting in which this problem can be investigated.

A prospective study was performed of 100 consecutive patients undergoing CEA. All patients underwent preoperative and postoperative assessment performed by an independent ophthalmologist, including visual acuity, retinal fundoscopy and 120-point visual field analysis. Quantitative and qualitative data on intraoperative embolization were obtained by intraoperative transcranial Doppler (TCD) monitoring and correlated with postoperative ophthalmological findings.

TCD identified intraoperative embolization in 92 per cent of monitored operations. Before operation 42 patients had a positive history of AF but only five had evidence of embolization on fundoscopy. A further six patients had fundoscopic evidence of embolization but no history of AF. After operation only one patient had evidence of intraoperative retinal embolization but this was peripheral and did not result in a deterioration in visual function Before operation there was no significant difference in visual field scores between the eyes ipsilateral and contralateral to the symptomatic carotid artery. After operation ipsilateral eye scores deteriorated while contralateral eye scores remained unchanged. This deterioration was sufficient to result in a statistically significant difference between the two sides in the absence of fundoscopic evidence of embolization.

This study has identified a new group of patients who experience 'silent' retinal embolization before CEA. Similar to silent cerebral infarction on computed tomography, silent retinal embolization may be associated with a poorer prognosis and merits further investigation. Fundoscopic evidence of intraoperative embolization during CEA is rare, but visual scores do deteriorate in the ipsilateral eye compared with the contralateral eye. This is a new finding and further investigation is indicated to determine whether this is a haemodynamic or transient embolic effect.

Duplex surveillance is not indicated following carotid endarterectomy

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Duplex surveillance is frequently performed following carotid endarterectomy to demonstrate restenosis or progression of contralateral carotid disease

A total of 305 consecutive patients (median age 67 years; 220 men) underwent carotid endarterectomy for symptomatic 60–99 per cent internal carotid stenosis. Preoperative duplex scanning identified contralateral internal carotid disease in 113 patients (33, 50–70 per cent; 34, 70–99 per cent; 46, 100 per cent). Patients were followed prospectively for a median of 36 (range 6–98) months, with duplex surveillance at 1 day, 1 week, 3, 6, 9 and 12 months, and yearly.

Twenty-three patients (8 per cent) developed symptoms (stroke in five, transient ischaemic attack (TIA) in 18) referable to the contralateral carotid artery at a median of 9 months Two contralateral strokes occurred on the day of operation; two were associated with pre-existing internal carotid occlusion; and in one case sudden stroke occurred when a pre-existing 90 per cent stenosis occluded during follow-up. Progression of contralateral carotid disease from less than 70 to 70–99 per cent stenosis occurred in 12 patients (4 per cent); three developed symptoms ($P = 0{\cdot}06$, all TIAs) and underwent endarterectomy.

Four (11 per cent) of 36 patients developing 50 per cent or greater restenosis, compared with 26 (10 per cent) of 269 not developing such restenosis, developed ipsilateral symptoms (13 strokes, 17 TIAs; P not significant).

Following carotid endarterectomy restenosis is rarely associated with symptoms; contralateral stroke is rare and is not associated with progressive internal carotid artery disease suitable for endarterectomy. This study has shown no benefit of surveillance with duplex scanning following carotid endarterectomy

Results of 100 cases of pulse-spray thrombolysis for peripheral limb ischaemia

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Pulse-spray thrombolysis (PST) is a relatively new technique for the treatment of limb ischaemia of recent onset. It has been shown to reduce significantly the time taken to achieve lysis and produces good early results. The intermediate-term outcome in 100 consecutive patients with acute and subacute limb ischaemia treated with PST with a follow-up interval of up to 3 years is presented.

Eighty per cent of limbs were classified as Fontaine 3 or 4 and 41 per cent had some degree of sensorimotor deficit. Seventy limbs were treated with PST alone and 30 had an additional infusion. In 69 cases an additional catheter-directed intervention was required.

The median duration of lysis was 125 (range 35–1260) min, and the median dose of recombinant tissue plasminogen activator used was 18 (range 4–61) mg. Complete radiological patency was achieved in 79 per cent of limbs and the post-thrombolysis ankle : brachial index scores improved by a median of 0·6 (range 0–1·1) ($P < 0{\cdot}001$, Wilcoxon paired test). At 30 days nine patients had died, seven had undergone amputation, ten had had further surgery and two had rethrombosed, giving an overall success rate of 72 per cent. The cumulative limb salvage rate at 30 months was 80 (standard error 7·6) per cent and the estimated cumulative patency rate was 68 (standard error 8·8) per cent

The incidence of major bleeding was 7 per cent and minor bleeding 23 per cent. There were no haemorrhagic strokes in this series but three ischaemic strokes occurred at 2, 9 and 12 days after thrombolysis.

PST achieves rapid and acceptably safe revascularization of acutely ischaemic limbs. These intermediate-term results demonstrate improved cumulative limb salvage and estimated patency rates on published results with conventional thrombolysis.

Accelerated thrombolysis with high-dose bolus tissue plasminogen activator is as safe and effective as low-dose infusions: results of a randomized trial

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Peripheral thrombolysis is an established treatment for the management of acute arterial and graft occlusion. Conventional low-dose therapy often necessitates prolonged infusion, excluding many patients with neurosensory deficit. High-dose bolus administration of tissue plasminogen activator (tPA) has the potential to reduce the duration of treatment.

One hundred patients requiring thrombolysis for acute leg ischaemia of less than 30 days' duration were randomized to receive either a high-dose bolus regimen of tPA (3 × 5 mg over 15–30 min, then 3·5 mg h^{-1} for up to 4 h, then 0·5–1·0 mg h^{-1}) or conventional low-dose therapy (0·5–1·0 mg h^{-1}). The groups were well matched for age, cardiovascular risk factors, duration and severity of ischaemia, and site, cause and length of occlusion.

The median duration of infusion for the high-dose group was 4 (range 0·25–46) h, compared with 20 (range 2–28) h for the low-dose group ($P < 0{\cdot}0001$, Mann–Whitney U test). There were no significant differences in other outcome measures: 30-day limb salvage rate was 78 per cent for high-dose *versus* 83 per cent for low-dose therapy, amputation rate 13 *versus* 5 per cent, death rate 9 *versus* 12 per cent, major haemorrhage 6 *versus* 7 per cent, stroke 0 *versus* 2 per cent, and distal embolization 6 *versus* 5 per cent.

High-dose bolus therapy significantly accelerates thrombolysis with tPA, treating 50 per cent of patients within 4 h, without increasing risks or compromising results. High-dose bolus infusions of tPA have the potential to be used for the initial treatment of most patients with acute limb ischaemia.

Vascular sealing with a novel autologous fibrin sealant

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A novel fibrin sealant (Vivostat Processor Applicator System), designed to be autologous in patients, has recently been developed as a haemostatic agent. It avoids the risks of transmission of bloodborne infective agents which are present with other commercially available sealants. This method of preparation and delivery has been used to test its properties as a vascular sealant in a randomized controlled study in pigs.

Biotinylated batroxobin is added to 60 ml patient plasma to produce 4–6 ml fibrin I solution. Biotinylated batroxobin is then removed before the coadministration of the fibrin I solution with a high pH buffer. This causes the fibrin I to polymerize, forming a physiological fibrin II clot. A spray system has been developed which provides enhanced mixing of the two components as they are applied to the target tissue. The entire automated process takes less than 30 min.

Fourteen Yorkshire white pigs (30–35 kg) had the left femoral artery exposed and were given 10 000 units heparin intravenously. A longitudinal arteriotomy (10 mm) was created and repaired with a knitted Dacron (Du Pont, Stevenage, UK) patch (12 mm) using six evenly spaced, interrupted 6/0 polypropylene sutures. In eight animals the patch was covered with the fibrin sealant (human origin) and in six haemostasis was obtained by the use of oxidized regenerated cellulose. After clamp removal, blood loss was calculated by spectrophotometric analysis of the haemoglobin content of the swabs. Arterial pressure was maintained constant by a Hartmann infusion throughout the procedure.

	Fibrin sealant	Oxidized regenerated cellulose	P*
Blood loss (ml)	8·6	269·9	0·001
Time to haemostasis (s)	187·5	472·5	0·04

Values are median. *Mann–Whitney *U* test

All arteries were patent at autopsy (10 days).

This novel autologous fibrin sealant is quick and easy to prepare and has been shown to be a superior haemostat to oxidized regenerated cellulose in this model of heparinized arterial bleeding.

Myoelectrical stimulation to augment arterial graft blood flow

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Early graft failure occurs in 10–20 per cent of femorodistal bypasses for critical ischaemia. Blood flow and surface thrombogenicity are determinants of infrainguinal graft patency. Low flow velocity and failure to respond to a hyperaemic challenge may predict graft failure.

Chronic electrical stimulation of muscles increases capillary density, maximal blood flow and resistance to fatigue. During muscle contraction blood flow increases. The effects of a single period of electrical stimulation of the gastrocnemius muscle on arterial graft blood flow in the early postoperative period were investigated.

Baseline graft blood flow after a 30-min rest was established by duplex Doppler ultrasonography in 16 patients who had recently undergone femorocrural reconstruction for critical ischaemia. The gastrocnemius muscle was then electrically stimulated for 15 min (pulse width 350 μs at 10 Hz) using a programmable pocket muscle stimulator. Blood flow measurements taken during stimulation and for 30 min afterwards were compared with flows in patients undergoing voluntary foot dorsiflexion exercises. No patient found muscle stimulation uncomfortable. During stimulation the mean (range) blood flow increased in 15 of 16 patients by 46 per cent, from 134·7 (32–262) to a peak of 196 (28–342) ml min^{-1} ($t = 7\cdot84$, $P < 0\cdot0001$, Student's *t* test), compared with foot dorsiflexion exercises during which mean flow increased by 4 per cent from 135 (30–282) to 140 (28–282) ml min^{-1}. Mean (range) blood flow was greatest at 5 min within ceasing stimulation at 175·8 (28–307) ml min^{-1} ($t = 5\cdot66$, $P < 0\cdot0001$). Significantly increased graft blood flow persisted for up to 20 min after stimulation. In one patient in whom there was no increase in flow, graft failure occurred within 30 days.

Electrically stimulated muscle contraction increases graft blood flow in the newly revascularized limb. Intermittent periodic stimulation may reduce the risk of graft failure in the early postoperative period. Failure to respond to this non-invasive hyperaemic challenge during graft surveillance may be of value in predicting poor outcome.

Comparative study of the effects of covering porcine renal artery origins with stents differing in size of strut and interstices

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There have been problems with securing the infrarenal end of endoprostheses. Little work has been performed to date on the effects of covering renal arteries with stents and on renal artery blood flow. The present model used 60–90-kg Large White pigs with arterial dimensions approaching those of humans. The study compared the effects of the 48-wire Wallstent and the Palmaz stent. Early work is in progress using the Memotherm.

Stents were placed over one or both renal arteries. Nine were covered with the Wallstent, nine with the Palmaz and three with the Methotherm, so far. Blood was taken for baseline urea and electrolyte estimation and full blood count determination Completion aortography was performed. After 6–8 weeks aortography was repeated. Intra-arterial blood pressure was measured, comparing the stented renal artery with the stented and unstented aorta. Blood was taken from the renal arteries for full blood counts and blood films to check for red cell fragmentation. Renal vein blood was taken for biochemical analysis. The kidneys and stented aorta were then sent for histological examination including scanning electron microscopy (SEM).

Two stents have been compared to date: the 48-wire Wallstent and the standard Palmaz stent. The Wallstent has finer struts than the Palmaz; they are more numerous and more regularly placed. Therefore the amount of renal artery ostium covered by the struts is not dependent on stent placement. However, the large struts and interstices of the Palmaz stent give great variability. Using SEM, in the best case none of the ostium is covered, and in the worst case 40 per cent is covered (where the elements meet). This compares to 34–38 per cent with the Wallstent. This appears to be significant in that there was no incident of macro- or micro-embolization with the Wallstent, with no significant differences between blood samples taken before and after stenting. There was no evidence of red cell fragmentation. With the Palmaz stent, however, one case of macroscopic renal damage occurred, and another animal had biochemical evidence of renal impairment. In all cases SEM revealed partial endothelialization of the stented aorta, but the renal arteries were fully patent and showed no signs of stenosis despite being crossed by at least one element in all cases. There was complete absence of red cells or platelet adhesion.

The new 48-wire Wallstent has properties which make it a good choice for coating with a view to endoprosthetic repair of aortic aneurysms. Covering renal arteries with the bare Wallstent in an animal model appears not to have any deleterious effect in the short term This work suggests that placement of stents with larger struts over renal arteries will require imaging methods to ensure that the ostium is not obstructed.

Non-restrictive external stenting reduces early medial and neointimal thickening in an experimental model of arteriovenous bypass grafting

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The long-term clinical success of autologous saphenous vein bypass grafts is limited by progressive medial and neointimal thickening in the graft and superimposed atherosclerosis. These changes may represent an adaptation by the vein to its insertion into the arterial system; one factor thought to be responsible is increased wall stress. The authors sought to reduce wall thickening by applying an external Dacron (Du Pont, Stevenage, UK) stent to experimental vein grafts in pigs. Three stent sizes were selected with respect to their influence on the initial expansion of the vein in response to arterial pressure: mildly restrictive, non-restrictive and oversized (5, 6 and 8 mm in diameter respectively).

Four weeks after graft implantation, total wall thickness was decreased by 33 per cent in 5-mm stents ($P = 0{\cdot}01$ *versus* unstented grafts) and by 60 per cent in 6- and 8-mm stents ($P = 0{\cdot}001$). Stented grafts had a thinner media compared with unstented grafts ($P = 0{\cdot}0001$ for all three stent sizes). Neointimal formation was reduced almost threefold by both 6- and 8-mm stents ($P = 0{\cdot}004$) but not by the 5-mm stent. As a result, the encroachment of the intima into the lumen was halved by both 6- and 8-mm stents ($P < 0{\cdot}02$ and $P = 0{\cdot}008$ *versus* unstented grafts respectively). Cell proliferation, detected by immunocytochemistry for proliferating cell nuclear antigen, was significantly reduced by all three stents in both medial and neointimal layers compared with unstented grafts ($P = 0{\cdot}001$).

These data show that external stenting of saphenous vein bypass grafts reduces smooth muscle cell proliferation and wall thickening. Oversized stents appear to favour more profound suppression of both medial and intimal thickening. Because wall thickness and final luminal size are thought to be of paramount importance in maintaining long-term patency, non-restrictive external stenting is likely to be of benefit. Moreover, the equal efficacy of the two oversized stents would obviate the need for precise size matching between the stent and graft, thereby greatly simplifying the surgical procedure.

A new modular approach to endoluminal grafting for abdominal aortic aneurysms

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Recent studies have demonstrated potential pitfalls and technical complications that can occur during endovascular stenting for abdominal aortic aneurysms (AAAs). Original prototypes have been developed for both straight and bifurcated stent systems which appear to resolve these limitations of the technique.

The straight device is composed of a tapered, fully supported nitinol stent, coated with a woven polyester fabric (permeability 2600 ml cm^2 min^{-1}). The production technique allows different diameters at either end to be selected and implemented, based on aneurysm morphology. The bifurcated nitinol device is a modular system. It is composed of three units, a proximal module with an inherent dual-passage interposition zone into which each iliac limb is anchored. This zone caters for variation in total aneurysm length between patients. Following deployment of the tapered proximal unit, the ipsilateral iliac limb is deployed after passage of a second delivery system coaxially using the guidewire of the original proximal module. The contralateral iliac limb is deployed after passage of a wire through the contralateral interposition zone within the proximal module. Both systems have been tested *in vivo* using a porcine model following creation of a prosthetic AAA. Devices were delivered and deployed under fluoroscopic guidance and aneurysm sac exclusion was confirmed on angiography and by incision into the prosthetic aneurysm. Chronic studies are under way to define long-term characteristics of the stent design before clinical application.

Deployment of both systems successfully excluded the aneurysm sac in all cases. Some angiographic irregularity of the luminal aspect of the devices was attributed to the fact that the nitinol stent lies within the graft material rather than supporting it externally, and not because of the accumulation of thrombus. This was confirmed at autopsy. Passage of a steerable guidewire through the contralateral interposition zone in the bifurcated device was achieved in each case without delay, and the total time for stenting in each case was less than 1 h.

This study confirms that a modular approach to transfemoral stenting of AAAs is feasible, and reported complications of other techniques appear to have been resolved.

Do scaling systems presently used in the hand–arm vibration syndrome accurately reflect disease severity as measured by objective tests?

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Approximately 500 000 workers in the UK are exposed to vibration and 20 000 suffer with moderate or severe hand–arm vibration syndrome (HAVS). Thus there is an increasing requirement for accurate diagnosis and assessment of severity.

The aims of this retrospective study were to assess whether the Taylor–Pelmear scale (TPS) and the Stockholm Workshop Scale (SWS) correlate with disease severity as measured by isotope limb blood flow (ILBF) and rewarming rates on cold provocation thermography (CPT).

The hospital records of 137 patients (135 men and two women, median age 51 (range 27–82) years) presenting during 1986–1995 for diagnosis and assessment of HAVS were examined. From the history, examination and blood tests, primary Raynaud's disease, other causes of secondary Raynaud's phenomenon and conditions mimicking HAVS were excluded and patients were graded on the TPS and SWS. Patients then underwent ILBF measurement, an investigation designed to detect reduced hand perfusion, and CPT, which is designed to detect exaggerated vasoconstriction in the fingers in response to cold.

Using non-parametric statistical analysis (Kruskal–Wallis analysis of variance) the increasing disease severity as graded by the TPS and SWS was found not to correlate with the objective tests of hand perfusion.

	ILBF	CPT
SWS	$P = 0{\cdot}53$	$P = 0{\cdot}25$
TPS	$P = 0{\cdot}93$	$P = 0{\cdot}53$

The TPS and SWS grading systems do not reflect disease severity and, if severity is to be accurately assessed, this must be done by means of objective testing of the circulatory system of the hand, preferably using tests of organic occlusion of the vessels and dynamic tests of vasospastic tendency. A new disease severity scoring system is required and this should be developed on the basis of objective investigations.

Relationship between cerebral oxygenation and blood pressure during carotid endarterectomy

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Near infrared spectroscopy can measure changes in the cerebral concentration of oxidized cytochrome oxidase (caa$_3$ — the terminal link in oxidative phosphorylation) during carotid endarterectomy (CE) and provide an objective assessment of cellular ischaemia following carotid clamping. Whilst it is widely believed that a rise in systemic blood pressure (BP) may be beneficial during CE there is no literature to support this. Thus changes in caa$_3$ concentration and systemic BP have been continuously recorded in patients undergoing CE under general anaesthesia ($n = 38$) or a regional local anaesthetic block ($n = 34$).

Following carotid occlusion caa$_3$ levels fell in 27 of 33 patients having regional anaesthesia and in 24 of 36 having general anaesthesia ($P = 0{\cdot}15$; three traces uninterpretable) but recovered within 3 min (autoregulation) in a greater proportion of patients having regional anaesthesia (19 of 27 *versus* eight of 24, $P < 0{\cdot}01$). While mean(s.d.) systemic BP before operation was the same in both groups of patients in whom caa$_3$ levels fell (114(2) mmHg) it was lower in patients having general anaesthesia before carotid clamping (99(3) *versus* 109(3) mmHg, $P < 0{\cdot}05$). Furthermore a rise in BP occurred more often in patients having regional anaesthesia (20 of 27 *versus* ten of 24, $P < 0{\cdot}05$) following carotid clamping (14(2) *versus* 1(2) mmHg, $P < 0{\cdot}001$) and there was a close correlation between the occurrence of a rise in systemic BP and autoregulation (increase *versus* no increase in BP: autoregulation 24 of 30 *versus* three of 13; $r = 0{\cdot}65$, $P < 0{\cdot}05$).

Despite these findings there was no correlation between either a fall in caa$_3$ or stump pressure and a rise in BP on clamping suggesting that neither cellular ischaemia nor low intracerebral perfusion pressure is directly responsible for autoregulation.

In conclusion, this study provides the first objective evidence that a rise in systemic BP is beneficial during CE and that this mechanism for cerebral autoregulation is preserved by regional but not general anaesthesia. Further investigation is required to establish the stimulus for these changes.

Popliteal vein reflux demonstrated by duplex ultrasonography is associated with delayed and non-healing of chronic venous ulceration

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Identification of patients with chronic venous ulceration who have a poor prognosis allows scarce hospital resources to be concentrated on managing the most intractable of ulcers The objective of the study was to determine the relationship between deep and superficial venous reflux and healing of chronic venous ulceration. A prospective study was carried out of 154 patients with chronic venous leg ulceration.

Patients underwent duplex ultrasonography by a consultant radiologist (P.L.A.) before initiation of compression therapy and were followed for 6 months.

At 24 weeks, 104 ulcers (67 per cent) had healed. There was no significant difference in the pattern of deep or superficial venous reflux between the healed and non-healed group except with respect to the popliteal vein (PV). In healed legs, 39 scans (38 per cent) indicated competence of the above-knee PV compared with five (10 per cent) in the non-healing group ($P < 0{\cdot}001$, χ^2 test). Similarly 44 scans (42 per cent) showed below-knee PV competence in the healed legs compared with only five (10 per cent) performed in legs remaining ulcerated ($P < 0{\cdot}001$, χ^2 test). Four (10 per cent) of 42 patients with competent, and 45 (44 per cent) of 103 with incompetent, above- and below-knee PVs failed to heal ($P < 0{\cdot}001$, χ^2 test; sensitivity 40 per cent, specificity 90 per cent, positive predictive value 44 per cent, negative predictive value 90 per cent).

PV incompetence is strongly associated with delayed and non-healing. The presence of incompetence at other sites had no effect on healing.

Single-layer *versus* four-layer bandaging in the treatment of venous ulcers: a randomized controlled trial

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Graduated compression is the most important element in the management of venous leg ulcers. Healing rates of 70–80 per cent in 12 weeks have been reported for a four-layer bandaging regimen which is capable of sustaining 40 mmHg at the ankle[1], but this has not been evaluated in a large randomized controlled trial. This trial compared the healing rates using a four-layer system (orthopaedic wool, crepe, Elset and Coban) with those employing a single-layer bandage (Granuflex Adhesive Compression Bandage) also capable of sustaining 40 mmHg at the ankle[2].

Some 200 patients with chronic venous leg ulcers and no detectable arterial disease or major concomitant illness were randomized to receive either the single-layer bandage or the four-layer system. The primary wound dressing was also randomized to either a knitted viscose or a hydrocolloid wafer. The third arm of this trial randomized patients to receive either oxpentifylline or placebo. The trial period was for 24 weeks or until all ulcers had healed. Bandages were changed weekly or as required.

Ninety-seven patients were allocated to the four-layer system, of whom 67 (69 per cent) healed in 24 weeks; 103 were allocated to the single-layer bandage, of whom 50 (49 per cent) healed in 24 weeks. The difference in healing rates was significant at the 95 per cent confidence level (odds ratio 2·39, 95 per cent confidence interval 1·33–4·29, $P = 0{\cdot}003$). Randomization to dressing and oxpentifylline or placebo was similar in the two groups. There was no interaction between dressing and bandages or bandages and oxpentifylline.

The four-layer system was significantly better than the single-layer bandage in healing venous leg ulcers.

1 Moffatt CJ, Franks PJ, Oldroyd M. *et al.* Community clinics for leg ulcers and impact on healing. *BMJ* 1992; 305· 1389–92.
2 Sockalingham S, Barbenel J, Queen D. Ambulatory monitoring of the pressure beneath compression bandages. *Care Science and Practice* 1990; 8: 75–9.

Outpatient varicose vein assessment: hand-held Doppler or duplex scanning?

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The clinical assessment of varicose veins is notoriously unreliable. More recently hand-held Doppler (HHD) ultrasonography has been advocated in the outpatient setting.

The aim of this study was to correlate HHD findings in a specialist venous clinic with colour duplex scanning by a consultant vascular radiologist (M W.).

Fifty-eight patients (44 women, 14 men) with primary (40 patients, 61 limbs) and recurrent (18 patients, 26 limbs) varicose veins aged 19–72 (mean 46) years were assessed by a consultant vascular surgeon using a HHD (8 MHz) probe. The saphenofemoral (SF), saphenopopliteal (SP) and midthigh perforator (MTP) junctions were assessed with patients in the standing position. They subsequently underwent colour duplex scanning of the same sites by a dedicated vascular radiologist (M.W.).

	Primary (*n* = 61 limbs)			Recurrent (*n* = 26 limbs)		
	SF	SP	MTP	SF	SP	MTP
Sensitivity	77	83	38	54	75	50
Specificity	91	93	86	92	72	67
Predictive value	94	83	67	84	54	60

Values are percentages

In patients presenting with primary varicose veins, HHD will miss 23 per cent of patients with saphenofemoral incompetence and 17 per cent of those with saphenopopliteal incompetence. Its ability to detect thigh perforators was poor in primary and recurrent veins. In patients with recurrent varicose veins, HHD was more unreliable and the authors would recommend colour duplex scanning before surgical intervention for varicose veins.

Systematic review of the morbidity and mortality of carotid endarterectomy

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Reported morbidity and mortality of carotid endarterectomy varies considerably. In an effort to explain the apparent heterogeneity of the operative risks of stroke and death, and to define risk factors for a poor surgical outcome, a systematic review was carried out of the published literature since 1980

Of 126 studies identified, only 51 reported the risks of surgery by indication. The overall mortality rate as a result of surgery for symptomatic carotid stenosis, based on 17 105 operations, was 1·6 (95 per cent confidence interval (c.i.) 1·3–1·9) per cent. The overall risk of stroke and death was 5·3 (4·4–6·1) per cent. The reported risks were related to study methodology. The risk of stroke and death was higher in prospective than in retrospective series (odds ratio (OR) 1·23, 95 per cent c.i. 1·1–1·4) and in studies in which outcome was assessed by neurologists as opposed to surgeons (1·36, 1·2–1·6)

Meta-analysis of risk factors within individual studies revealed the following predictors of stroke and death: asymptomatic *versus* symptomatic carotid stenosis (OR 0·61, 95 per cent c.i. 0·5–0·7); amaurosis fugax *versus* cerebral symptoms (0·47, 0·3–0·6); female sex (1·89, 1·1–3·0); systolic blood pressure greater than 180 mmHg (1·82, 1·4–2·4); occlusion of the contralateral carotid artery (1·91, 1·4–2·7); stenosis of the ipsilateral carotid syphon (1·56, 1·0–2·4). Stroke *versus* transient ischaemic attack, current smoking, diabetes, ischaemic heart disease and carotid plaque ulceration did not predict operative risk.

A simple prognostic model based on the number of additional risk factors in patients with symptomatic carotid stenosis was validated using data from the European Carotid Surgery Trial. The risk of stroke and death within 30 days of surgery was 2·0 (0·4–5·8) in patients with no risk factors, increasing to 18·5 (13–25) per cent in those with more than three risk factors (χ^2 for trend, $P < 0{\cdot}00001$).

Much of the heterogeneity in reported risks of carotid endarterectomy appears to be due to differences in study methodology and case mix. The risks can be predicted for individual patients using a simple, independently validated, prognostic model.

Efficacy of carotid endarterectomy for 30–69 per cent symptomatic carotid stenosis in the European Carotid Surgery Trial

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The European Carotid Surgery Trial is a multicentre randomized trial of carotid endarterectomy for patients with recently symptomatic carotid stenosis. In 1991, interim results showed that surgery was beneficial in patients with greater than 70 per cent stenosis and harmful in those with less than 30 per cent stenosis. Randomization continued in patients with 30–69 per cent stenosis, but was stopped in 1994. At least 4 months' follow-up is now available on 1590 patients (99·4 per cent) in this category. Mean follow-up is 4·5 years.

Outcome was analysed separately for patients with 30–49 and 50–69 per cent stenosis. The risk of death or stroke lasting longer than 7 days within 30 days of trial surgery was 8·0 (95 per cent confidence interval 5·5–11·1) per cent in the 30–49 per cent group and 7·9 (5·8–10·4) per cent in the 50–69 per cent group. In both groups, all-cause mortality was non-significantly higher in patients randomized to surgery compared with those randomized to medical treatment alone. Surgery had an adverse effect on stroke-free survival ($P < 0{\cdot}05$, long rank test) between 0 and 2·3 years in the 50–69 per cent stenosis group and between 0 and 3·4 years in the 30–49 per cent stenosis group. Beyond these times there were no significant differences.

These data do not support the use of carotid endarterectomy in patients with recently symptomatic 30–69 per cent carotid stenosis.

Carotid endarterectomy in the elderly patient

P. T. McCollum, A. Da Silva and L. De Cossart for the Vascular Surgical Society of Great Britain and Ireland Audit Committee

A prospective study of 112 patients aged 76 years or more, undergoing carotid surgery in the UK and Ireland, was performed to evaluate the risk of vascular surgery in this age group within the Society.

Fifty-nine surgeons (range 2–39 cases each) were sampled and all patients aged 76 years or more undergoing surgery over a 6-month period (from March to August 1994) were included in the study. All incomplete and inconsistent data were rechecked. Indications for surgery were transient ischaemic attack (37·5 per cent), amaurosis fugax 25·9 per cent), cerebrovascular accident (18·8 per cent) and 'other' (17·8 per cent). Preoperative arteriography was performed in 50·9 per cent. Mean ipsilateral stenosis was 82 (range 50–99) per cent. Twenty-six per cent of patients had preoperative neurological consultations. Shunts were used in 66·1 per cent, tacking sutures in 39·3 per cent, drains in 74·1 per cent and patches in 57·1 per cent of cases.

At 30 days there was one death (0·9 per cent) and one postoperative cerebrovascular accident (0·9 per cent). Sixteen per cent of patients had one or more complication, usually minor. Statistical analysis showed no significant differences in outcome or risk factors when compared with a younger group of 589 patients having carotid surgery during the same period.

A combined stroke and death rate of 1·8 per cent at 30 days for the elderly group was lower than that for the younger group, but this was not significant. This large study suggests that members of the Vascular Society for Great Britain and Ireland currently perform carotid surgery with a highly acceptable risk of stroke in the elderly population. As life expectancy in these patients is generally approximately 5 years, such surgery is cost effective and offers the probability of a much reduced risk of stroke in selected patients

Serial surveillance imaging does not alter outcome following carotid endarterectomy

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The long-term outcome (median follow-up 49 (range 2–120) months) of the operated and non-operated carotid artery was studied in 243 patients undergoing 260 carotid endarterectomies (CEAs), 166 of whom underwent serial postoperative imaging surveillance by either duplex scanning or intravenous digital subtraction angiography (median 36 (range 6–84) months). The aim was to see whether a clinical and imaging surveillance programme influenced clinical practice.

Including perioperative events, cumulative freedom from ipsilateral stroke in the operated carotid artery was 86 and 82 per cent at 5 and 10 years respectively, giving a mean incidence of ipsilateral stroke of 1·8 per cent per annum Cumulative freedom from occlusion or severe (more than 70 per cent) recurrent stenosis was 87 and 78 per cent at 5 and 10 years, giving a mean incidence of significant disease recurrence of 2·2 per cent per annum. Cumulative freedom from stroke in the non-operated carotid artery was 96 and 86 per cent at 5 and 10 years, giving a mean incidence of stroke of 1·0 per cent per annum. Overall, no redo CEAs were performed in this series, late strokes (in operated and non-operated carotid arteries) were rarely preceded by transient ischaemic attacks, while onset of late cerebral ischaemic symptoms usually preceded recognition of significant disease progression.

This surveillance programme failed to prevent any late stroke and did not alter clinical management in any case. Accordingly, patients are now reviewed at 6 weeks and thereafter discharged with instructions to return immediately if symptoms recur.

Duplex scanning can be used alone in the assessment of patients for carotid endarterectomy

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The present guidelines on the management of carotid artery disease are based on the angiographically defined degree of stenosis. This retrospective study assessed the accuracy of duplex scanning in defining the degree of stenosis, compared with the angiographic method used in the European Carotid Artery Trial

One hundred patients (median age 71 (range 42–84) years; 71 men, 29 women) with symptomatic carotid artery disease (stroke, 38; transient ischaemic attack, 38; amaurosis fugax, 52) were investigated by both carotid duplex ultrasonography and arch aortography.

Considering all 198 carotids (99 symptomatic, 99 asymptomatic) visualized on both duplex scanning and angiography, duplex had a positive predictive value of 98 per cent, a negative predictive value of 98 per cent and an accuracy of 97 per cent in defining significant stenosis compared with an angiographic standard. There was no statistical difference in the findings of duplex ultrasonography and angiography ($\chi^2 = 1{\cdot}22$, $P = 0{\cdot}25$, McNemar test). One patient developed a major complication following angiography and died from mesenteric ischaemia.

In general, duplex ultrasonography provides an accurate method of assessing patients for carotid endarterectomy, and can be adopted alone as a safe alternative to angiography.

Carotid endarterectomy in the UK and Ireland

P. T. McCollum, A. Da Silva and L. De Cossart for the Vascular Surgical Society of Great Britain and Ireland

A prospective study of 709 patients undergoing carotid surgery in the UK and Ireland was performed to evaluate the performance of vascular surgeons.

Fifty-nine surgeons (range 2–39 cases each) were sampled and all patients undergoing surgery over a 6-month period (from March to August 1994) were included in the study. All incomplete data were rechecked and only nine records were discarded because of incomplete data, leaving 700 cases for analysis. None of these nine patients had a postoperative cerebrovascular accident (CVA). Indications for surgery were transient ischaemic attack (35·9 per cent), amaurosis fugax (23·3 per cent), CVA (21·4 per cent) and 'other' (19·6 per cent). Preoperative arteriography was performed in 54·9 per cent. Mean ipsilateral stenosis was 82 (range 30–99) per cent. Thirty-one per cent of patients had preoperative neurological consultations. Shunts were used in 67·6 per cent, tacking sutures in 40·1 per cent, drains in 71·9 per cent and patches in 54·4 per cent of cases.

At 30 days there were nine deaths (1·3 per cent) (four cardiac, three neurological, two other). There were 15 postoperative CVAs (2·1 per cent); 19·0 per cent of patients had one or more complications, usually minor Statistical analysis showed no independent risk factor for CVA other than seniority of the surgeon. In particular, peroperative shunting, preoperative CVA, preoperative contralateral occlusion and monitoring had no independent effect on the peroperative stroke rate.

A combined stroke and death rate of 3·4 per cent for the series was obtained at 30 days for all patients. This large validated study suggests that members of the Vascular Society of Great Britain and Ireland currently have very acceptable morbidity and mortality rates for performing carotid surgery. Continued audit is required to ensure that this quality of service does not deteriorate.

A short-limb bifurcate stent graft system for endovascular repair of abdominal aortic aneurysm: early experience

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If endovascular repair of abdominal aortic aneurysm is to become more widely applicable, a reliable bifurcate graft system is required.

A self-expanding short-limb bifurcate graft system lined by z stents and anchored proximally by a Gianturco stent has been deployed in 16 patients (14 men, two women; median age 73 (range 60–84) years). Indications for endovascular repair were an aneurysm at high risk of rupture for which conventional repair was considered unduly hazardous (severe ischaemic or valvular heart disease, ten patients; severe respiratory disease, six, hostile abdomen, five; renal failure, four; malignant disease, three). The uncovered Gianturco stent was deployed across the origin of the renal arteries in 13 of 16 patients. The aneurysm was successfully excluded in 13 of 16 patients. There have been no deaths or conversion to open repair. All 13 aneurysms remained excluded at follow-up (median 20 (range 2–46) weeks) and decreased in size by a median of 7 (range 20 to −5) per cent. None of the aneurysms with a leak sealed spontaneously. There were no renal artery occlusions or deterioration in renal function following the procedure. Median serum creatinine concentration was 110 (74–238) μmol l^{-1} before operation *versus* 114 (range 75–266) μmol l^{-1} at 22 (range 2–46) weeks after operation (*P* not significant). Complications included a stroke during an attempt to correct a proximal leak via the brachial artery. Occlusion of an iliac limb occurred in two patients, and in one of these the whole graft assembly subsequently thrombosed; neither patient has required intervention for ischaemia.

Initial results in this high-risk group have been acceptable. The long-term results, upon which the success or failure of this technique depend, remain to be established.

Microembolization during endovascular aneurysm repair

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Endovascular aneurysm repair has been advocated as a 'minimally invasive' alternative to conventional aneurysm surgery. However, owing to the presence of layered thrombus within the aneurysm sac, it is possible that endovascular techniques may result in embolization of visceral and peripheral arteries. Initial clinical reports have documented a 5 per cent incidence of massive microembolization following deployment of intraluminal aortic prostheses.

Lower limb microemboli were quantified in 15 patients undergoing conventional (eight patients of median age 71 years, median aneurysm size 5·4 cm, five straight and three bifurcated grafts) and endovascular (seven patients of median age 74 years, median aneurysm size 5·6 cm, six aortoiliac and one straight grafts) aneurysm repair by insonation of the superficial femoral artery with a 2-MHz Doppler probe. Emboli were detected as high-intensity short-duration signals on the background Doppler trace. Differentiation of air emboli (AE) from particulate emboli (PE) was achieved by calculation of the sample volume length (SVL) for each embolus ($n = 3806$), which is the product of embolic velocity and duration (determined by Wigner analysis). Prior experiments had determined that a SVL of less than 1·4 cm represented particulate embolization.

	PE during graft insertion	Total PE	Total AE	Total emboli
Endovascular	84 (42–182)*	127 (101–182)	244 (90–361)	371 (195–489)*
Conventional	15 (2–36)	41 (18–183)	81 (29–124)	163 (110–252)

Values are median (interquartile range). *$P < 0{\cdot}05$ (Mann–Whitney *U* test)

Three patients with more than 100 particulate emboli developed trash feet.

These data demonstrate that peripheral microembolization is significantly higher during endovascular aneurysm repair than during conventional surgery. Visceral embolization during intraluminal aneurysm surgery may result in multiple organ failure, and methods to prevent embolization must be developed before endovascular aneurysm surgery is widely adopted.

Multi-seeded three-dimensional computed tomographic angiography: a novel technique for assessing suitability for endovascular stent grafting of abdominal aortic aneurysm

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Conventional axial (CA) computed tomographic assessment of abdominal aortic aneurysm (AAA) does not provide all the necessary information to define patient suitability and the potential for technically successful stent graft deployment. The aim of this study was to compare CA scanning with multi-seeded shaded surface rendering (SSR) in infrarenal AAA.

A total of 18 patients underwent spiral computed tomography using a Siemens Somatom Plus-S scanner. CA and SSR were compared for their ability to assess the following factors: (1) aneurysm size; (2) dimensions and angulation of the proximal and distal necks; (3) relationship to and patency of the visceral and lumbar arteries; (4) tortuosity and patency of the iliac arteries; and (5) the presence and extent of mural thrombus and vascular calcification.

The techniques were comparable for measurement of luminal dimensions, display of mural thrombus and vascular calcification. SSR alone allowed appreciation of the length and angulation of the aneurysm necks, the tortuosity of the iliac vessels and the relationship to the renal arteries. Neither technique demonstrated patent lumbar arteries but SSR regularly showed patency of the inferior mesenteric artery and also, in two patients, accessory renal arteries.

Endovascular grafting of AAA requires detailed imaging. SSR is the technique of choice to define patient suitability for the procedure and those likely to have a successful outcome.

Mid-aortic syndrome with renovascular hypertension presenting in early childhood

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Mid-aortic syndrome (MAS) is an uncommon condition involving stenosis of the abdominal aorta and its branches, and presents a challenging problem in children. The aim of this retrospective study was to analyse experience of 14 patients with MAS presenting with renovascular hypertension, to consider the treatment options and to undertake a critical review of the terminology used, the aetiology, pathogenesis and treatment options.

Fourteen children with MAS were treated between 1975 and 1994. All had hypertension, four had neurofibromatosis and three had Williams' syndrome.

Seven children were treated successfully with antihypertensive medication alone. Percutaneous transluminal angioplasty was attempted three times, with poor results. Seven patients underwent surgical reconstruction, because of renal function impairment or refractory hypertension, with good results in six; one died. Techniques to revascularize the kidneys included thoracoabdominal to infrarenal aortic bypass with renal artery reimplantation, splenorenal bypass, gastroduodenal to renal bypass, aortorenal bypass and autotransplantation.

MAS should not be confused with inflammatory aortitis; it is probably a congenital and/or genetic condition. The timing of surgery is the most important decision in treating children presenting with MAS and refractory hypertension. Every effort should be made to delay surgery until the child reaches the age of 5–6 years. The use of a thoracoabdominal aortic bypass may be the definitive procedure of choice after this age. If the child comes to surgery during early childhood, splenohepatorenal bypasses can be used if the coeliac axis is not compromised, and autotransplantation should be considered.

Ambulatory outpatient angioplasty

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Revascularization by percutaneous transluminal angioplasty (PTA) is usually performed as an inpatient procedure after preliminary angiography. A prospective assessment was made of 139 consecutive patients undergoing ambulatory outpatient PTA selected by preliminary duplex scanning. This study assesses the accuracy of duplex scanning compared with angiography at PTA and the safety of ambulatory outpatient PTA.

Over a 52-month period, 168 procedures were studied. The indication for PTA was claudication in 128 cases, critical ischaemia in 22 and graft stenosis in 18. The *Table* shows the agreement between duplex scanning and angiography, and technical and haemodynamic success (increase greater than 0·1 in ankle systolic pressure index).

	Iliac	SFA	Popliteal	Graft	Overall
No. of procedures	30	108	12	18	168
Agreement	23 (77)	102 (94)	12 (100)	18 (100)	155 (92)
Technical success	26 (87)	96 (89)	10 (100)	18 (100)	150 (89)
Haemodynamic success	21 (70)	77 (71)	7 (58)	15 (83)	120 (71)

Values in parentheses are percentages. SFA, saphenofemoral artery

There were six complications (4 per cent), all recognized at the time of PTA (four significant haematomas, one distal embolization and one myocardial infarct). A further five patients were admitted because of unforeseen organizational problems.

Duplex scanning is an acceptably accurate screening tool in selecting patients for angioplasty. Ambulatory angioplasty is a feasible and safe procedure. These findings will improve both patient comfort and cost–benefit.

Does β-adrenergic blockade limit the growth rate of abdominal aortic aneurysm?

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Two separate American studies have indicated that β-blocker therapy may reduce, by about half, the growth rate of abdominal aortic aneurysm (AAA), this effect being most marked for AAAs of 5·0 cm or more in diameter. The influence of β-blockade on the growth rate of AAA in patients considered unfit for surgery was investigated as part of the UK Aneurysm Study and Small Aneurysm Trial.

The trial coordinators monitored AAA growth and blood pressure at 3–6-monthly intervals in 100 patients with a median initial AAA diameter of 5·0 (range 3·6–8·5) cm. The mean(s.d.) age of the patients (79 men, 21 women) was 70·3(4·3) years; the median length of follow-up was 21 months. Only 18 patients were being prescribed β-blockers; 78 were not and four were uncertain of their medication.

First inspection of the data showed that the growth rates appeared linear with no evidence of acceleration for increasing diameter: linear regression confirmed this finding in 87 of the 100 patients. At the time of reporting all aneurysms had reached a diameter greater than 5 cm. The median AAA growth rate was 0·41 (range 0–1·85) cm per year. For the 18 patients taking β-blockers the median growth rate was 0·41 (range 0–1·1) cm per year ($P = 0{\cdot}82$). Similarly neither systolic nor diastolic blood pressure was associated significantly with AAA growth rate.

This study provides no support for the hypothesis that β-blockade limits AAA growth rate, but more conclusive evidence must be obtained from randomized trials.

Myocardial infarction following abdominal aortic aneurysm repair

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The incidence of perioperative myocardial infarction is highest following surgery for peripheral vascular disease than for any other form of non-cardiac surgery. A prospective study was conducted to determine the incidence of perioperative myocardial infarction in patients undergoing both elective and emergency abdominal aortic aneurysm (AAA) repair. Diagnosis of perioperative myocardial infarction is difficult as fewer than half the patients with perioperative myocardial infarction do not have chest pain. In 20 per cent of these patients the electrocardiographic (ECG) changes are not significant, thereby limiting its diagnostic accuracy. Measurement of creatinine kinase MB (CKMB) concentration is highly sensitive in detecting perioperative myocardial infarction.

Postoperative CKMB concentration was measured in 183 patients who underwent AAA repair over a 33-month period. Forty patients (21·9 per cent) had raised CKMB levels (range 12–103 mg l^{-1}; normal value less than 8 mg l^{-1}). Of these, 21 patients had ECG changes of either myocardial ischaemia or infarction. Half the patients with raised CKMB levels had a documented history or preoperative ECG changes suggestive of ischaemic heart disease, hypertension or congestive cardiac failure. There were 12 deaths; ten patients had a fatal myocardial infarction and nine of these were known to have ischaemic heart disease.

This study confirmed that the presence of ischaemic heart disease is a poor prognostic factor in major surgery for peripheral vascular disease. Clinicians should be aware of a high incidence, in this study found to be 22 per cent, of silent myocardial infarction following major vascular surgery.

Higher surgical training in vascular surgery: is the complex module sufficiently flexible?

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Shortened training, reduced junior doctors' hours and increased demand for vascular surgeons have significant implications for vascular surgical training in the UK. The aim of this study was to audit recent (1989–1995) vascular operative experience of higher surgical trainees during single-year periods before successful appointment to consultant posts in vascular surgery. Experience gained within this period was compared with guidelines issued recently by the Vascular Advisory Committee (VAC). Total numbers of 'level 3 – complex module' cases undertaken by the unit were also audited for the same period.

All vascular operative details in this unit have been prospectively collected on to a computerized database over the past 10 years. Details of surgery undertaken during a year of higher surgical training, by five trainees subsequently appointed to consultant posts in vascular surgery, were analysed. Results are given as median (range) numbers of procedures performed as principal surgeon or assistant.

	Procedures per trainee per annum		VAC guidelines	
	Assistant	Principal	Unit	Trainee
AAA (elective)	10 (7–22)	11 (3–13)	20	
AAA (rupture)	2 (1–4)	4 (2–7)		5
Aortoiliac or bifemoral	3 (2–8)	3 (1–5)	20	
Extra-anatomic bypass	7 (4–10)	11 (6–12)	20	
Femoropopliteal or tibial bypass	10 (3–15)	22 (18–35)	40	10 distal
Thrombectomy or graft revision	4 (0–8)	6 (3–14)		
Embolectomy	3 (1–5)	11 (7–12)		
Amputation	2 (1–6)	11 (8–17)		
Carotid endarterectomy	9 (7–18)	7 (3–13)	20	10
Total no. of arterial cases	57 (38–98)	90 (73–125)	>100	

AAA, abdominal aortic aneurysm

Median numbers of 'level 3 – complex module'-designated cases undertaken by the unit per annum (1990–1994) were: renal artery reconstruction, one; supracoeliac aneurysm, three, thoracoabdominal aneurysm, two; upper limb arterial reconstruction, seven; atrioventricular malformation, one; paediatric vascular problems, one; carotid body tumours, two.

This audit confirms that operative vascular surgery criteria recommended by VAC guidelines are adequately met by trainees and training units. Low total numbers of designated 'complex' cases mitigate against development of a 'complex vascular module' *per se*. Structured and coherent training is to be encouraged, but rigid adherence to the modular concept of 'level 3' training is likely to diminish the broad base of experience gained by trainees. Flexibility at this stage is advocated.

Endoluminal repair of abdominal aortic aneurysm: preliminary experience

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Endoluminal abdominal aortic aneurysm (AAA) repair involves the insertion of an intraluminal prosthetic graft via the femoral or iliac arteries, with the aim of excluding the aneurysm sac from the circulation. This technique avoids intraperitoneal manipulation, reduces aortic occlusion time and may be a possible solution to reducing mortality in high-risk patients.

From January 1994 to July 1995 a total of 82 patients was assessed for endovascular repair. From this cohort, 16 patients (15 men, one woman) underwent endoluminal AAA repair. The median age was 73·5 (range 61–82) years and the median AAA diameter 5·5 (range 5·0–6·9) cm. An aortoaortic (tube) graft repair was attempted in seven patients, a tapered aortoiliac reconstruction in eight and bifurcated graft in one. There were three initial failures requiring conversion to open repair. Additional procedures included iliac artery angioplasty in two cases, coil embolization of an associated common iliac aneurysm in one and a femorodistal vein bypass in one. The median operating time was 180 (range 95–270) min and the median blood loss 1000 (range 500–2000) ml. Median hospital stay was 7 (range 4–21) days. Complications included one early death, one patient with reversible acute tubular necrosis, one who required prolonged ventilation and two with buttock claudication. Follow-up with colour duplex scanning and contrast-enhanced computed tomography demonstrated three perigraft leaks (two proximal, one distal). One further distal leak developed 12 months after operation. Two patients underwent late conversion, one due to aneurysm expansion as a result of a persistent proximal perigraft leak (6 months after operation) and the other due to a new distal leak detected at 1 year.

It is concluded that endovascular repair of AAA is feasible but not free of significant complications. These procedures may be long, complicated and associated with major blood loss. In view of a conversion rate of 30 per cent, this technique may not be suitable for 'unfit' patients. A randomized trial of conventional *versus* endovascular AAA repair is required before widespread use of the endoluminal technique.

Treatment of residual iliac aneurysm by graft stents following surgery for ruptured abdominal aortic aneurysm

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These two case reports demonstrate the efficacy of graft stents in the treatment of iliac aneurysm following surgery for ruptured abdominal aortic aneurysm (AAA).

Two patients, one of whom had already undergone repair of an AAA, presented with aortic rupture. Both had successful surgery by the insertion of a bifurcated woven polyester graft to the origins of widely spaced common iliac arteries (CIAs). At the time of surgery both CIAs were noted to be aneurysmal in both patients. One patient necessitated a jump graft to the external iliac artery for thrombosis of the right CIA aneurysm.

Subsequently both patients presented with symptomatic enlargement of CIA aneurysms. The patient who had the jump graft had retrograde embolization of the right CIA aneurysm The left CIA aneurysm was treated by insertion of a 10 mm × 10 cm graft stent (Endopro; Cragg) via a 10-Fr sheath. The second patient who also had a symptomatic CIA aneurysm, had a 12 mm × 10 cm graft stent (Endopro; Cragg) inserted. Both patients were discharged the following day. At follow-up, computed tomography showed no evidence of leak around the graft stents, which were functioning well at 6 and 8 months.

The surgical treatment for ruptured AAAs involves repair of the ruptured segment rather than definitive correction of all arterial pathology. It is rare for iliac aneurysms to cause symptoms following aortic surgery; however, if they do, insertion of a graft stent is a quick and safe alternative treatment, with a short stay in hospital compared with surgical correction.

Stroke during intra-arterial thrombolysis: a survey of experience in the UK

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A questionnaire survey of members of the Thrombolysis Study Group has been conducted to study stroke occurring during intra-arterial thrombolysis (IAT) for acute vascular occlusion. At present, data are available from nine centres, which between them have treated 1157 patients with IAT. There have been 27 clinically evident strokes reported (2·3 (range 1·5–22·0) per cent). Mortality and residual morbidity were high.

Twelve patients were fully heparinized at the time of stroke, six were on aspirin and three were taking warfarin. The majority of cases had infusion of recombinant tissue plasminogen activator (20 of 27); five had streptokinase and one urokinase Ten strokes were haemorrhagic, eight non-haemorrhagic, with nine being of unknown type because no computed tomography, angiography or post-mortem examination was performed. Contrast-enhanced CT was the most commonly employed diagnostic aid (17 of 27), with angiography seldom having a place. Cardiac echo was performed on seven occasions with a zero pick-up rate for cardiac thrombus or valve disease. Risk factors included seven patients with hypertension, 11 current smokers, nine with cardiac arrhythmia, three with past myocardial infarction, two with carotid disease and one diabetic. Only five of 27 patients had a past history of stroke, with none having any sign of this at the time of treatment. Fourteen strokes happened during IAT, but ten occurred 24 h to 12 days after lysis was completed In four of 27 cases there were technical problems during thrombolysis, including catheter thrombus and significant arterial damage.

A significant number of the strokes attributed to thrombolysis occur after, rather than during, infusion and often in the setting of administration of other antithrombotic drugs, which are themselves associated with stroke. More effort should be made to diagnose the occurrence and type of stroke definitively Contrast-enhanced CT is currently the most useful modality for achieving this. Current smoking, hypertension and cardiac arrhythmia seem to be significant risk factors.

This study clearly identifies the risk of stroke during IAT using the techniques and protocols commonly used in UK institutions. These values should now form the basis for informed consent in the UK.

Setting the 'gold standard' for peripheral thrombolysis

B. D. Braithwaite for the Thrombolysis Study Group

Intra-arterial thrombolysis (IAT) is an established primary treatment of acute arterial and graft occlusion. Methods for reporting treatment outcome vary in the many published series and in the relatively few randomized trials on IAT. This, combined with the heterogeneous nature of patients requiring IAT, makes comparison of treatment methods difficult, so that it is almost impossible for one unit to compare results with another. To address this problem, a group of radiologists and surgeons have prospectively collected information on IAT, entering data in a standard format on to a specially commissioned computer database, with a capability for analysis of angiograms

In the first year of computerized data collection, 166 events of thrombolysis were performed on 104 men and 62 women of mean age 68 (median 69, range 19–92) years. Sixty-one per cent presented with rest pain, 27 per cent with incapacitating claudication and 10 per cent with ischaemic ulceration. The mean duration of ischaemia was 17 days (median 4 days, range 2 h to 1 year). Ninety-three native vessels and 73 grafts, mainly polytetrafluoroethylene, were occluded The underlying cause was thrombus in 66 per cent of cases and embolus in 19 per cent; the remainder could not be differentiated. Thrombolysis was performed with recombinant tissue plasminogen activator (rtPA) using a variety of methods including low-dose, high-dose bolus or pulse-spray infusions. The mean dose of rtPA was 24 (median 21, range 3–156) mg and infusions lasted a mean of 20 (median 17, range 1–144) h. Complete lysis was achieved in 49 per cent of cases, clinically useful lysis in 28 per cent, lysis but no runoff in 15 per cent and lysis failed in 8 per cent (92 per cent lysis rate). Immediately after lysis, angioplasty was performed in 31 per cent of patients undergoing infusion, aspiration embolectomy in 5 per cent and atherectomy in 1 per cent Open surgery, not including amputations, was performed on 26 per cent of patients. At 30 days the limb salvage rate was 79 per cent, amputation rate was 13 per cent and 8 per cent died. Major haemorrhage occurred in 11 per cent of patients having infusion, and there were two strokes (one embolic and one haemorrhagic).

The close cooperation between different hospitals and specialties has quickly produced information with which the group participants can audit their own results and set treatment standards for outcome and complications associated with IAT with rtPA. The size of the database has also provided a system for predicting outcome and complications related to patient and treatment factors.

Who needs thrombolysis? Aspiration without tears

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An evaluation was made of the role of acute primary percutaneous aspiration thrombectomy in the treatment of lower limb ischaemia.

Eleven procedures were conducted in ten patients with acute or subacute lower limb arterial occlusion. Antegrade puncture was conducted in eight patients and retrograde puncture in two. Catheter reversal with iliac and femoral aspiration was conducted in one patient. Two patients were on warfarin at the time of treatment. One patient had had a recent gastrointestinal haemorrhage, which precluded thrombolysis.

Introducers (7 or 8 Fr) with detachable hubs were used in combination with guiding catheters or butchered Van Andel catheters. Catheter sizes of 5–8 Fr were available. The treated vessels included the iliac, femoral, popliteal and below-knee arteries. Adjuvant thrombolysis was administered in four patients. Complete success alone or in combination with adjuvant angioplasty was achieved in five patients. Primary success with secondary failure at 3–5 days occurred in one patient twice. Improvement in radiological appearance without gross improvement in clinical status of the critical limb, even with adjuvant thrombolysis, occurred in the other four patients.

This is an excellent technique for rapid treatment of acute lower limb thromboembolic disease. There are specific benefits for use of the technique in patients in whom thrombolysis is contraindicated and also in those who are fully anticoagulated at the time of acute incident.

Integrated vascular surgical and interventional radiology training

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Since the introduction of balloon angioplasty, vascular surgery and interventional vascular radiology have been converging and the increasing number of endovascular therapeutic options implies that this trend will continue. The potential synergy between surgeons and radiologists could be encouraged by appropriate changes to the existing training programmes of both radiologists and surgeons.

This concept has been tested by the creation of a vascular radiology fellowship funded from regional contingency training funds. The objectives were to provide a vascular surgical trainee with the opportunity to receive specific interventional vascular radiological training and to assess the feasibility of such a cooperative training programme. Additionally, opportunities to improve the clinical, research and training links between vascular surgery and radiology were identified and projects initiated to address specific problems.

Radiology trainees are expected to perform approximately 50 diagnostic angiograms before they are deemed to have sufficient experience to begin learning interventional techniques. Over a 6-month period the vascular radiology fellow performed 85 diagnostic angiograms, 18 angioplasties and four stent placements under direct supervision of a consultant radiologist. The major training deficiencies encountered were lack of familiarity with the radiographic equipment, catheters, guidewires and endovascular therapeutic techniques. One problem identified was the relatively limited communication between vascular surgeons and radiologists, and a project was started to design and implement an improved clinical data communication system to integrate with the existing vascular surgical database (VASDAT)

The experience has shown that vascular surgical training can usefully be augmented by specific training in fluoroscopic radiographic imaging, diagnostic angiography and percutaneous endovascular techniques. Such training should be integrated with a clinical or research post in vascular surgery rather than as a full-time radiology trainee, and should aim to provide experience of at least 100 procedures. Similarly, dedicated vascular radiology trainees should be encouraged to attend vascular surgical outpatient clinics, ward rounds and operations. Such training also has the potential to improve communications and encourage joint research projects, to evaluate the increasing number of endovascular techniques.

Does more mean better? Success and complications of peripheral angioplasty

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The success and complication rates of peripheral angioplasty were correlated with the number of procedures performed annually by a centre

Data were obtained from the Royal College of Radiographers' angioplasty audit. Ninety-three centres performing a total of 4906 procedures were included. Centres were grouped according to the number of procedures performed annually The average success and complication rates of these groups were compared with the site and type of lesions treated within each group Indications for treatment, as well as the age and relative health of patients, were also compared.

The proportion of iliac and saphenofemoral artery stenosis or occlusion treated by each group was similar. The success rate was significantly higher in centres performing 100–199 procedures annually. Complication rates did not differ significantly In general, lesions treated by centres performing fewer procedures were less severe.

Success rates are highest in centres with a moderate volume of cases per year, but complication rates do not vary according to the volume of work.

E-selectin as a predictor of restenosis following peripheral arterial angioplasty

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This study was designed to evaluate E-selectin as a predictor of restenosis following angioplasty.

Experimental studies have shown that endothelial dysfunction is an early event preceding restenosis. Monocytes and neutrophils have been shown to bind to damaged endothelium via cell adhesion molecules (CAMs). E-selectin is a CAM that is expressed only on activated endothelial cells. Its ligands are expressed on monocytes and neutrophils. The selectins are involved in capturing leucocytes and tethering them to the endothelium. E-selectin has been found to exist in a soluble form, which may represent a marker of endothelial damage and may be a precursor of smooth muscle proliferation.

Some 40 patients undergoing peripheral arterial balloon angioplasty had blood sampled before the procedure E-selectin concentration was measured in serum using an enzyme-linked immunosorbent assay. At follow-up angiography, ten patients had restenosed at 1 year.

There was a significant difference in mean baseline serum E-selectin levels in patients who restenosed compared with those who did not (64·6 (range 58·2–82·2) units *versus* 51·8 (range 34·1–59·8 units; $P < 0{\cdot}01$, Mann–Whitney U test).

Endothelial activation with subsequent adherence of white blood cells is an important step in restenosis. An increased level of shed serum E-selectin has been demonstrated in patients destined for restenosis. The authors suggest that this work further supports a role for white blood cell–endothelial interaction in restenosis following angioplasty.

Presenting symptom influences outcome following carotid endarterectomy

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Outcome-based standards have been set for carotid endarterectomy. However, outcome is dependent on many factors, including patient-related variables.

A total of 460 consecutive patients undergoing carotid endarterectomy for symptomatic 60–99 per cent internal carotid stenosis were followed clinically and by duplex surveillance prospectively at 3, 6, 9 and 12 months and then yearly for a mean of 40 months.

Multiple logistic regression analysis was performed, taking death and stroke as dependent variables and entering 20 independent variables into the model. A history of crescendo transient ischaemic attack (TIA) ($P = 0{\cdot}003$, $P = 0{\cdot}0002$) and female sex ($P = 0{\cdot}02$, $P = 0{\cdot}0001$) was associated with both death and stroke respectively within 30 days of operation. Death between 1 and 36 months was associated with ischaemic heart disease ($P = 0{\cdot}03$) and diabetes ($P = 0{\cdot}04$), whereas stroke was associated with small internal carotid external diameter ($P = 0{\cdot}02$).

Life-table analysis confirmed an association between presenting symptom and outcome.

Presenting symptom	Survival rate at 36 months (%)	Stroke rate at 36 months (%)
Amaurosis fugax	98	0
TIA	84	5
Transient stroke	66	13
Established stroke	85	8
Progressive stroke	77	27
Crescendo TIA	67	26

Thus rates of survival and avoidance of stroke were significantly higher in patients presenting with amaurosis fugax than in those with all other presentations ($P < 0{\cdot}01$). Similarly, patients presenting with crescendo TIA had a significantly worse prognosis than others ($P < 0{\cdot}05$).

Presenting symptom significantly determines outcome following carotid endarterectomy. This should be considered in both patient selection and comparison of patient series.

Carotid and vertebral artery transluminal angioplasty study

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Clinical trials have demonstrated the benefit of surgery for severe carotid stenosis, but there is still significant morbidity from the surgical procedure. Percutaneous transluminal angioplasty (PTA) has the advantage of avoiding general anaesthesia and trauma from surgical incision, and may cost less. PTA is widely used for coronary and peripheral vascular disease, but has not yet gained acceptance for carotid stenosis.

An overview was carried out of all known series of PTA for atherosclerotic carotid artery disease ($n = 447$), which suggests that PTA carries a risk of any stroke at the time of the procedure of less than 5 per cent and of major stroke of less than 2 per cent. Angiographic complications occurring without neurological symptoms included carotid occlusion, dissection and rupture. The technical success rate improved to 90 per cent. Follow-up angiography showed remodelling with restoration of satisfactory lumen calibre in most cases, consistent with transcranial Doppler studies of middle cerebral artery blood flow showing significant improvements in cerebral haemodynamics.

Technological advances have recently enabled the treatment of eccentric calcified lesions at the carotid bifurcation (previously unsuitable for PTA) by endovascular stenting. Some lesions, such as very tortuous stenoses, remain unsuitable. The benefits in the prevention of subsequent stroke are uncertain.

The authors have therefore established an international multicentre randomized trial known as the Carotid And Vertebral Artery Transluminal Angioplasty Study with the primary aim of determining the comparative risks and benefits of carotid and vertebral PTA. Patients suitable for surgery are randomized between PTA and surgery; those not suitable between PTA and medical treatment. Individual centres randomize patients in their own 'grey area'. PTA is carried out with balloon catheters and/or stents, according to the preference of individual radiologists. Some 180 patients have been randomized to date. The results of the trial should determine whether carotid PTA is a valid alternative to surgery.

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Correspondence

Surgical treatment for morbid obesity

Sir

In response to the correspondence (*Br J Surg* 1995; 82: 1701–2) published on this article (*Br J Surg* 1995; 82: 732–9) I have the following comment.

It is not necessary to divide between the pouch and the fundus of the stomach after a vertical banded gastroplasty to prevent late disruption of the staple line. It is only necessary to use a four-layer stapler. Then, with the double-gloved finger behind the staple line, it is only necessary to penetrate the tissue that lies between the two middle staple lines with the needle tip of the electrocautery and switch on the current for approximately 1 s until a burn appears around the cautery point. If this is repeated approximately every 3 or 4 mm, the result is a series of full-thickness injuries which in time becomes a 'spot weld' at the staple line.

No method, not even dividing the two compartments, can prevent early dehiscence. This method can prevent long-term dehiscence and, in the 3 or 4 years I have been using it, I have had no staple line breakdowns in approximately 20 patients.

This method was inspired by a report of an Australian surgeon who, working in the outback using dingoes as an experimental animal, found that horizontal gastroplasty staple lines could be made to outlast the voracious eating habits of these animals if an older model stapler was used, screwed down as tightly as possible on the stomach and allowed to remain for 30 min before setting the staples. I concluded that full-thickness necrosis is necessary to prevent late separation. I have forgotten this hero's name and, if he reads this, I hope he will accept my congratulations. If I remember correctly, he did the research at his own expense.

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Bladder injury during laparoscopic abdominoperineal resection

Sir

In their case report (*Br J Surg* 1995; 82: 1207) Mr Williams and colleagues describe a bladder injury inflicted during the perineal dissection of a laparoscopic abdominoperineal resection for rectal cancer. They comment that laparoscopic dissection in the optimum plane is more difficult because of insufficient retraction of the abdominal rectum with the laparoscopic instruments. They also refer to the loss of tactile contact between the abdominal and perineal operators as a major disadvantage. To compensate for the incomplete abdominal dissection, they propose that a more extensive perineal dissection will be necessary.

We do not believe in this strategy, as it is no easier to mobilize the difficult rectum from the perineal approach. There is also strong evidence that precise dissection of the rectal fascia is the best way to reduce local recurrence. If the laparoscopic dissection cannot be properly advanced below the prostate, as must have been the case in this case report, then the laparoscopic method is inadequate.

We have performed two complete laparoscopic abdominoperineal resections, while in another two patients the procedure was converted to an open operation because the dissection could not mobilize the rectum with the same precision expected from the open operation. With this limited experience we have found no need for tactile contact with the abdominal operator once the laparoscopic dissection has been adequate. But then we have long since abandoned simultaneous dissection in favour of two surgeons in partnership completing the stages in sequence. For those surgeons who rely on tactile contact for the perineal dissection, we are convinced that a laparoscopic instrument can serve the same purpose as the hand of the abdominal surgeon.

We believe that it is in the best interest of our patients and the future of laparoscopic bowel surgery that those who attempt laparoscopic abdominoperineal resection convert to open operation if the dissection cannot be carried out totally with precision. The rectum which is difficult to manage will have to await new and better laparoscopic methods.

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Authors' reply

Sir

We would like to thank Professor Smedh and colleagues for taking interest in our report. Their group, like ourselves, obviously has limited experience with this particular technique and clearly had the same problem during dissection. I would agree with their urge for caution and the need to convert if there are problems. This is a basic policy for all laparoscopic surgery. Can we also add that the patient reported remains alive and well some 3 years after operation?

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Lateral subcutaneous sphincterotomy for treatment of anal fissure in children

Sir

I was interested to read the article by Messrs Cohen and Dehn on lateral subcutaneous sphincterotomy (LSS) in children (*Br J Surg* 1995; 82: 1341–2). They have shown that LSS is an effective treatment for anal fissure in this group of patients. The article recommends LSS as the first-line treatment, adding that 'anal dilatation is an inappropriate operation in paediatric practice'. I accept that anal dilatation has been poorly standardized in adult practice; there are additional problems of size in a paediatric population. Nevertheless, a formula can be used to estimate the normal anal calibre in children of differing sizes. I accept that anal dilatation in adults, if injudiciously performed, can cause serious sphincter damage and incontinence. The same *may* be true in children but, as they point out, this is not known. More importantly, the late effects of LSS in children are also unknown. Anal dilatation can cause damage; LSS *always* causes damage. Whether the amount of damage caused to children by either procedure is important, and whether such damage is more likely with one or other procedure, is simply not known. I think it is premature to say that anal dilatation has no place.

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Single-stage treatment for malignant left-sided colonic obstruction: a prospective randomized clinical trial comparing subtotal colectomy with segmental resection following intraoperative irrigation

Sir

The SCOTIA Study Group should be congratulated for completing, collating and publishing the results of this long-awaited and worthwhile clinical study (*Br J Surg* 1995; 82: 1622–7). However, while there now seems to be a strong argument for a single-stage procedure, we disagree that 'segmental' resection following intraoperative irrigation is the preferred option except when there is caecal perforation or if synchronous neoplasms are present in the colon, when subtotal colectomy is 'more appropriate'. Their own data suggest an appreciable incidence of synchronous disease, the management of which needs further consideration. Indeed, synchronous neoplasia (benign and malignant) was twice as common after subtotal colectomy. As we appreciate that neoplastic lesions are notoriously difficult to detect in distended proximal colon, when should a 'postoperative surveillance' programme (as the authors suggest) be started to detect metachronous or 'missed' synchronous cancers?[1] We recently managed an 80-year-old man who, 10 months earlier (elsewhere), had undergone on-table lavage and primary anastomosis for an obstructing carcinoma of the mid-sigmoid. He presented with intermittent vomiting which was initially thought to be adhesive, but colonoscopy revealed a malignant stricture in the ascending colon. He underwent a radical right hemicolectomy and, fortunately, the stage of this 'missed' tumour was also Dukes B.

A Medline search (1990–95) has identified 13 reports allowing a comparison between subtotal colectomy and on-table lavage (*Table 1*). While significant synchronous pathology might not be detected in the limited colectomy specimens after on-table lavage, the reports do not mention the incidence of such 'missed' synchronous lesions despite accruing, and presumably following up, their patients over periods of 4–6 years[2].

Table 1 Data from recent reports documenting experience with subtotal colectomy and on-table lavage

Data	Subtotal colectomy	On-table lavage
No. of reports	7	6
No. of patients	174	110
30-day mortality rate (%)	8 (5)	5 (5)
Synchronous cancers* in specimen (%)	5–11	n.a.

*Includes malignant polyps. n.a., Not available

Finally, while fervour for subtotal colectomy may have been tempered by the purported incidence of diarrhoea after operation, this does not appear to be a 'real' problem[3–4], and we question the choice of initial procedure in the paraplegic patient as even in a randomized trial clinical common sense must be our first consideration.

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1 Bat L, Neumann G, Stemesh E. The association of synchronous neoplasms with occluding colorectal cancer. *Dis Colon Rectum* 1985; 28: 149–51.
2 Stewart J, Diament RH, Brennan TG. Management of obstructing lesions of the left colon by resection, on-table lavage and primary anastomosis. *Surgery* 1993; 114: 502–5.
3 Stephenson BM, Shandall A, Farouk R, Griffith GH. Malignant left-sided large bowel obstruction managed by subtotal/total colectomy. *Br J Surg* 1990; 77: 1098–102.
4 Arnaud JP, Bergamaschi R. Emergency subtotal/total colectomy with anastomosis for acutely obstructed carcinoma of the left colon. *Dis Colon Rectum* 1994; 37: 685–8.

Authors' reply

Sir

Thank you for the opportunity to reply to Dr Evans and colleagues who highlight a number of important points about functional outcome and the management of synchronous and metachronous neoplasms in patients presenting with malignant left-sided colonic obstruction.

It was against a background, 5 years ago, of increasing use of single-stage operations but uncertainty with regard to outcome and applicability in reported series, that a randomized trial was initiated by the SCOTIA group. This has shown that functional outcome was superior when the policy was to carry out (radical) segmental resection when appropriate rather than subtotal colectomy. Having randomized a patient before operation the pragmatic nature of the study design and the analysis by 'intention to treat' removed pressure on surgeons to perform what they considered an inappropriate procedure.

The size of our study precludes worthwhile comment on the difference between the frequency of detection of synchronous neoplasia in the two groups, but good surgical technique will minimize the risk of missing synchronous tumours. We agree that neoplastic lesions are notoriously difficult to detect in obstructed proximal colon but we would not recommend that the colon be examined at this stage. We advocate full mobilization of the colon so that it lies outwith the abdominal cavity for irrigation. At the end of colonic lavage the colon returns to normal calibre with a clean lumen, and we have detected previously impalpable cancers during final manipulation of the prepared colon. The experience of Dr Evans and colleagues in a patient with a missed synchronous cancer after segmental resection underlines the importance of the technical aspects of 'on-table' irrigation as preliminary to segmental colectomy. Furthermore, it is a simple and rapid matter to pass a flexible endoscope peroperatively after on-table irrigation and we would now recommend this when circumstances permit. Failing this, a colonoscopy should be performed within the first 3–6 months after potentially curative operation. The shortening of the colon after resection of the left and sigmoid colon greatly facilitates colonoscopic surveillance after operation.

The optimal follow-up of patients with colorectal cancer is the subject of some debate, and a subtotal colectomy with ileorectal anastomosis does not eliminate the risk of metachronous cancer or the need for surveillance after operation. Resectional surgery in excess of conventional radical cancer surgery, be it elective or emergency, should be limited to circumstances where the need is established.

We perceive a contradiction in the final paragraph of Dr Evans *et al.* in that, if diarrhoea after subtotal colectomy is not a 'real' problem, why do they question the use of this operation in a paraplegic patient?

The SCOTIA Study is the only reported prospective randomized study to have addressed these issues and, while the outcomes in both groups were acceptable, we stand by the conclusion that subtotal colectomy be reserved for the specific indications of synchronous neoplasia and caecal rupture.

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Book reviews

Venous Disorders. A Manual of Diagnosis and Treatment

G. Belcaro, A N. Nicolaides and M. Veller (eds).
244 × 168 mm. Pp. 194. Illustrated. 1995. London: W. B. Saunders. £19·95.

In a field of growing interests and specialization this is a potentially worthwhile book. Acute and chronic venous disease, including thromboembolic and lymphatic diseases, are covered. Anatomy and investigations are well described. There are useful sections on the swollen limb, uncommon venous disorders and drugs used in venous disease. The format is attractive, the text simple and is usefully divided into sections with clear colour illustrations. In a specialty that desperately needs to be moving into the realms of science it is discouraging to see so much eponymous nomenclature lingering in venous anatomy, clinical tests etc., but that is a criticism which applies to most venous literature.

For a small book it has a lot of authors who have in common a link with the St Mary's Vascular Laboratory, a source of many recent valuable advances in knowledge, particularly of venous investigations This does, however, give the text a certain bias and at times a disproportionate emphasis; for instance, extensive coverage of investigations, including several pages on air plethysmography, in contrast to the half page allocated to the treatment of that most difficult and costly of venous problems, ulceration. The discussion is at times a little disorganized for those seeking a more detailed exposition of difficult issues. The references are well distributed across the world literature. There are also a number of clinically important omissions; for instance, activated protein C resistance, the most important factor in thrombophilia, is not mentioned, nor is the importance of preventing fungal infections in lymphoedema. There is no discussion of techniques for subfascial perforator ligation, including endoscopic methods. Some aspects of management will not find favour with many UK surgeons, e.g. stripping of the short saphenous vein, full length stripping of the long saphenous vein or the application of sclerotherapy at the time of vein surgery.

The authors do not define their target readership and I wonder whether they have given the matter sufficient thought There is a particular need to provide good reading material for technicians, sonographers and specialist nurses who are making such important contributions to venous care, and each will find some areas of interest. Undergraduates may find it useful, but it is too superficial for postgraduates an attractive, useful, but somewhat patchy book.

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ABC of Breast Diseases

J. M. Dixon (ed.). 297 × 210 mm. Pp. 74. Illustrated. 1995. London: BMJ Publishing Group. £15.

Michael Dixon has gathered a large number of mainly British contributors for this volume which was first published as a series of articles in the *British Medical Journal.* The book sensibly opens with chapters on indications for referral to breast clinics and benign breast disease, reflecting that even in specialist centres 90 per cent of all referrals do not have malignant disease. It then continues to cover breast cancer in all its aspects, including clinical trials, psychological care and reconstructive surgery. Although obviously designed to appeal to a wide medical audience, this book is readable and well illustrated. There is ample information for the surgical trainee as it covers all one needs to know in a general sense. The experts will find it handy to have on the bookshelf for the occasional enquiry, and to show to those in training and paramedical staff who have queries.

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Arterial Aneurysms – Diagnosis and Management

M. Horrocks (ed.). 252 × 192 mm. Pp. 246 Illustrated 1995. Oxford: Butterworth–Heinemann. £55.

This book, which comprises 19 chapters and 246 pages, is made up of contributions by selected authors, virtually all surgeons, and virtually all from British centres. The perspective and detail of various topics related to aneurysm epidemiology, pathophysiology, locations, management techniques and complications is quite exhaustive and informative, and is supported by appropriate referencing. Nearly every educative feature has been addressed, keeping in mind that the book is partly aimed at the higher surgical trainee in vascular surgery. Minor criticisms of the book apply to some deficiencies (management of coagulopathy, reconstruction techniques to overcome various technical problems), a tendency for repetition in different chapters, and idiosyncrasies of the authors which may soon prove obsolete. There is a lack of uniform operating-room protocol, for example, heparinization, prophylactic antibiotics, maintenance of renal function (where conflict exists between anaesthetic and surgical contributors) and some weaknesses (thrombolysis only by streptokinase, no radiology of stable ruptured aneurysms). There are also a couple of typographical errors. This volume should be a valuable addition to the bookshelf of those dealing with aneurysms not involving the intracranial and aortic arch areas and, because of the huge amount of information of a widely dispersed nature, it fills a gap in the market, the authors have achieved their goals. Some subjects are rapidly evolving (endovascular repair) or are not detailed enough and a few readers may be mildly frustrated by these small difficulties.

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Lymph Node Surgery in Urology

J. P. Donohue (ed.). 240 × 158 mm. Pp. 163 Illustrated. 1995. Oxford: Isis Medical Media. £49.95.

Lymph node surgery was one of five topics discussed in depth at the International Society of Urology meeting in Sydney, Australia, in September 1994 and, although it has taken a year to produce, this book does provide the most up-to-date information on lymph node surgery in urology. Unfortunately, in a book of 163 pages, the word 'control' occurs once, and the term 'randomised clinical trial' twice. This is not so much a reflection on the book, but on the current state of urological oncology. Despite the high and increasing incidence of urological malignancy, there has been a failure of urologists to rid themselves of preconceived ideas as how best to treat urological cancer and to enter patients into randomized controlled clinical trials. This has resulted in the general conclusion, seen in so many of the 16 chapters in this book, that lymph node surgery is of prognostic rather than therapeutic value Despite this, the book should be required reading for all urologists and oncologists.

G. Williams

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British Journal of Surgery 1996, 83, 574

Notices and announcements

24 April 1996
British Association of Surgical Oncology — Breast Surgeons Study Day Meeting
Solihull, UK
Information: Mrs V. Hall, Administrator, BASO, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

25–26 April 1996
2nd Liverpool Hepatobiliary Masterclass
Liverpool, UK
Information: J. O'Leary, Training Manager, MASTER Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

29 April–1 May 1996
Practical Endovascular Techniques
Leicester, UK
Information: Dr K. Reddy, Course Organiser, Radiology Department, Medway Hospital, Gillingham ME7 5NY, UK

1–2 May 1996
1st Association of Coloproctology M62 Course
Huddersfield, UK
Information. Mr J. Hill, Consultant Surgeon, Department of General and Colorectal Surgery, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK

7–9 May and 19–22 November 1996
European Course on Laparoscopic Surgery
Brussels, Belgium
Information· Administrative Secretariat, Conference Services, Avenue de l'Observatoire, 3 bte 17, B-1180 Bruxelles, Belgium

12–15 May 1996
29th Annual Meeting of the Pacific Association of Pediatric Surgeons
Singapore
Information: Secretariat, Academy of Medicine, 16 College Road, Singapore 0316

15–18 May 1996
7th International Symposium on Pediatric Neuro-Oncology
Washington D. C., USA
Information: E. Paine, George Washington University, Office of CME, Washington D. C. 20037, USA

16–17 May 1996
International Symposium on Breast Reconstruction
Chester, UK
Information: D. McGeorge, Department of Plastic and Reconstructive Surgery, Countess of Chester Hospital, Chester CH2 1UL, UK

20–22 May 1996
Trauma and Critical Care '96 - Point/Counterpoint XV
Boston, Massachusetts, USA
Information: Carol Williams, Trauma Department, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60 611, USA

22–25 May 1996
25th Meeting of the European Histamine Research Society
Antwerp, Belgium
Information: G Van de Vyver, Department Geneeskunde, University of Antwerp, Universiteitsplein 1, B-2610 Antwerpen, Belgium

30 May–1 June 1996
Surgical Infection Society — Europe
Paris, France
Information: Professor P. Frileux, Scientific Secretariat, Department of General Surgery, Hôpital Laennec, 42 rue de Sèvres, 75 007 Paris, France

6–7 June 1996
Head and Neck Course 1996 — Hypopharyngeal Cancer
Hong Kong
Information: Head and Neck Course Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

7 June 1996
Difficult and Controversial Issues in Vascular Surgery
Saltash, Cornwall, UK
Information: Mr S. Ashley, Vascular Surgical Unit, Derriford Hospital, Plymouth PL6 8DH, UK

12–15 June 1996
International Association of Pancreatology
Mannheim, Germany
Information: Mr A. L. Warshaw, IAP Secretary, Massachusetts General Hospital, 15 Parkman Street, WAC 336, Boston, Massachusetts 02 114, USA

16–22 June 1996
38th Annual World Congress of the International College of Angiology
Köln, Germany
Information· D. M. Rossignol, Executive Director, International College of Angiology, 5 Daremy Court, Nesconset, New York 11 767, USA

23–26 June 1996
4th International Congress of the European Association for Endoscopic Surgery
Trondheim, Norway
Information: Congress–Conference A/S, PO Box 7609 Skillebekk, N-0205 Oslo, Norway

26–29 June 1996
CAR'96 – Computer Assisted Radiology 10th International Symposium and Exhibition
Paris, France
Information: Professor H. U. Lemke, Technical University Berlin, Institute for Technical Informatics, Sekr. CG FR 3-3, Franklinstrasse 28–29, D-10587 Berlin, Germany

27–28 June 1996
Surgical Research Society
Birmingham, UK
Information· Ms L. Hopwood, University Department of Surgery, Royal United Hospital, Bath B15 2TH, UK

29 June–3 July 1996
7th Annual Training Course for Clinicians: Practical Nutritional Support
Southampton, UK
Information: Mr. B. Moran, Institute of Human Nutrition, University of Southampton, Bassett Crescent East, Southampton SO16 7PX, UK

5–6 July 1996
Current Status of Surgical and Interventional Procedures for the Management of Aortic Aneurysm, Reno-Vascular Disease and Carotid Stenosis
Stratford-upon-Avon, UK
Information: Mrs L. de Cossart, Consultant Surgeon, Countess of Chester Hospital, Liverpool Road, Chester CH2 1UL, UK, or Dr J. Dyet, Consultant Radiologist, Hull Royal Infirmary, Anlaby Road, Hull HU3 3KZ, UK

7–9 July 1996
Joint Meeting of British Oncological Association in association with Royal College of Radiologists, British Institute of Radiology and British Society for Cell Biology
Cardiff, UK
Information· Meeting Secretariat, BOA 1996, 4 Cavendish Square, London W1M 0BX, UK

8–10 July 1996
Tripartite meeting of the Association of Coloproctology of Great Britain and Ireland, The Section of Coloproctology of the Royal Society of Medicine, American Society of Colon and Rectal Surgeons, Section of Colon and Rectal Surgery of the Royal Australasian College of Surgeons, Colorectal Surgical Society of Australia
London, UK
Information: Confrex, Conference Secretariat, 145 Islingword Road, Brighton, Sussex BN2 2SH, UK

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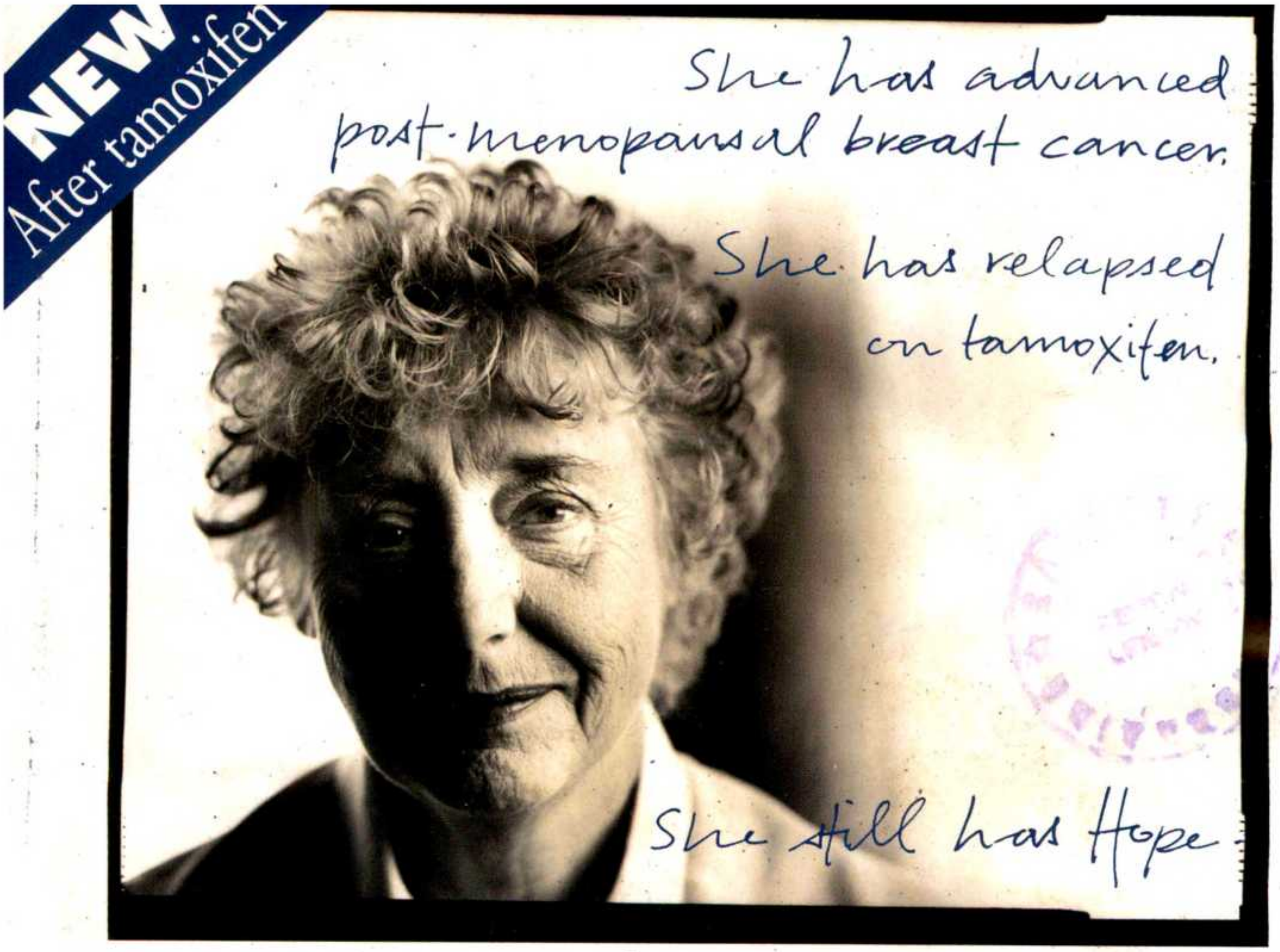
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95/4936(E) Issued September 1995

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